PROCEEDINGS

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VOLUME THE FIFTIETH *JANUARY TO DECEMBER 1957*

(SESSION OCTOBER 1956—SEPTEMBER 1957)

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1

Section of Experimental Medicine and Therapeutics

President—E. E. POCHIN, M.D., F.R.C.P.

[*May* 7, 1956]

SYMPOSIUM ON ANTI-TUMOUR AGENTS

First Session: Cytostatic Agents

Chairman—E. E. POCHIN, M.D., F.R.C.P.

Dr. Walter Davis (Chester Beatty Research Institute): *Chemical Structure and Biological Activity of the Cytostatic (Alkylating) Agents*

The chemotherapy of cancer presents the chemist with a different problem from that which faces those tackling the chemotherapy of the microbial diseases for we are all the time attempting to attack the tumour which is, more correctly, the effect rather than the cause of the pathological condition. Whereas the criterion of effectiveness of drugs being used against parasites or bacilli, for example, is simply their ability to kill or prevent reproduction of a foreign organism, the anti-tumour drug must be able to inhibit the growth and ultimately to destroy or disperse a tumour that in so many aspects of its behaviour and metabolism is scarcely distinguishable from the normal tissues from which it has sprung. This presents an immediate and practical problem of a test system capable of guiding the synthetic programme by giving indications of comparative effectiveness of each new drug that is made. Ideally what is wanted is some quantitative comparative test that can either compare equal activity at different dose levels or, alternatively, greater or less activity of similar doses of different drugs. In this present field we labour under the constant difficulty that test systems—and it is generally agreed that there is no test system better than experimental tumours for screening drugs of this type—are not very susceptible to providing graded quantitative results. For example, several compounds are now known which completely inhibit the Walker rat carcinoma, so that it is difficult to discriminate between them by their action on this tumour. On the other hand the Crocker sarcoma 180 is almost unaffected by a number of drugs which do appear to have some potential clinical application against Hodgkin's disease and chronic leukæmias. It is against this background that we shall attempt to discuss correlation of chemical structure with biological activity and therefore we shall sometimes be guilty of making what are more strictly subjective than statistical estimates of differing effectiveness of closely related compounds.

The measure of biological activity of these drugs is their power to inhibit the transplanted Walker rat carcinoma.

All the compounds that we are discussing here are chemically classed as alkylating agents but we should stipulate that they do not all produce the same biological effects and it is probable that even where the same type of effect is observed it would be unwise to assume that the same mechanism of action is involved. But the fact that these compounds are all capable of chemical reaction under physiological conditions does make it worth while recalling Ehrlich's classical theory of chemoreceptors that are blocked by reaction with drugs. A great deal of time has been devoted to *in vitro* studies of alkylation reactions between these drugs and functional groups that are present in living tissues and they are certainly capable in many cases of alkylating amino groups, carboxylic acid and phosphoric acid groups, for example, that occur abundantly in nucleoprotein. It is possible to build speculative theories that this type of chemical reaction is responsible for the observed biological effects, as for example the chromosomal aberrations, so frequently seen in tissue that has been treated with these drugs.

At any rate, this approach—the possibility of chemical reaction with naturally occurring functional groups—does provide the organic chemist with some rationale for investigating other types of reagents, capable of attaching themselves chemically under physiological conditions. Within any one series, the smaller structural changes that lead to a variation in biological activity can also provide a guide to the organic chemist for fruitful research. The type of alkylating agent that we shall be mainly discussing is the nitrogen mustards since we have devoted most time to their study. Early in the last war the studies of the possible effects of nitrogen mustard as a war gas (Fig. 1) led to the observation of its effect on the leucocytes which, in turn, led to its quite useful application in the treatment of Hodgkin's disease and the chronic leukæmias (Philips, 1950).

Because there were clinical difficulties associated with the use of HN2, a search was begun for a drug that was as effective against the lymphadenopathies but more moderate in its side reactions. This led to the development of the aryl as distinct from alkyl-halogenoalkyl-

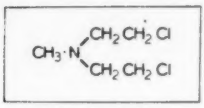


FIG. 1.—HN2.

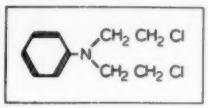


FIG. 2.

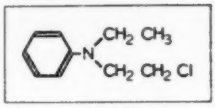


FIG. 3.

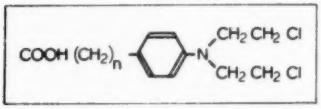


FIG. 4.—CB 1348 (n = 3).

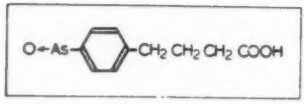


FIG. 5.

amines as potential anti-tumour drugs (Fig. 2) and this constitutes the first major structural change that resulted in a profound modification in the characteristics of the resulting drugs. Whereas the dichloroethylalkylamines were vesicant compounds that could only be administered by careful intravenous injection, the corresponding aryl compounds were mild enough for oral administration (Matthews, 1950). Chemically the distinction between these two series centres on the considerable difference in basicity of the parent amines and consequently difference in the reactivity of the chlorine atom. Throughout the nitrogen mustard group in both aryl and alkyl series, the most essential structural feature is undoubtedly the so-called bifunctionality. None of the many monochloroethylamines (Fig. 3) that have been tested have been found to have any activity whatsoever against experimental tumours. There has been much speculation on the significance of the need for the two chloroethyl arms to which the early theory of "cross-linking" made an important contribution (Goldacre *et al.*, 1949), but apart from asserting the need I do not intend to discuss its significance here.

Within the aryl-halogenoalkylamine series a very good correlation was soon established between chemical reactivity of the molecule and biological activity. For example, alteration in the *para*-substituents of the nitrogen mustard derived from aniline (Fig. 2) could be used either to increase or decrease the reactivity of the chloroethylamine group (Ross, 1949). Those substituent groups such as methyl, methoxy, or amino, which are electron-donating, increase the chemical reactivity—which can be conveniently determined by the hydrolysis rate of the compound—and produce active compounds. Electron-attracting substituents like chlorine, unionized carboxyl, phenyl or nitro reduce the hydrolysis rate to a very low order, and correspondingly, the compounds are inactive. Of course, these changes do more than merely affect the basicity of the nitrogen and hence the reactivity of the chlorine. The introduction of a basic amino group or a carboxylic (acidic) group into the molecule is bound to alter the conditions under which the drug might be adsorbed, whilst the latter group, in particular, profoundly alters the aqueous solubility of the drugs.

This introduces the conception that the part of the molecule other than the chloroethylamine group may be so chosen that whilst perhaps neither enhancing nor detracting from the fundamental activity of the drug it may greatly influence its arrival at its site of action. It was with this aim in view that the carboxyalkyl derivatives of the aniline mustard (Fig. 4) were synthesized, the introduction of the terminal carboxyl group having, as well as its acidic property, a solubilizing influence on the molecule. Within this series there appears to be an interesting variation amongst the five members of the series that have been made and tested. The first member derived from *p*-aminobenzoic acid, is of a low order of chemical reactivity, but still comes within the range that is associated with biological activity. The other members of the series (Fig. 4; n = 1–4) derived from *p*-aminophenylacetic acid (n = 1), propionic acid (n = 2), butyric acid (n = 3) and valeric acid (n = 4) all of which have a high and similar chemical reactivity, show a quite significant alternation in their level of biological activity. The most active member of the group is di-2-chloroethylaminophenylbutyric acid (n = 3) (now fairly well known as CB 1348) (Everett *et al.*, 1953). For two reasons it is tempting to ascribe this high level of activity to the specific structure of the molecule. Firstly in his study of trypanocidal drugs, Eagle found the most active one in a similar series of carboxyalkylphenyl arsenoxides (Fig. 5) was the butyric acid derivative, and secondly when we synthesized a comparable series of phenoxyalkyl compounds (Davis *et al.*, 1955) it was the phenoxypropionic acid derivative (Fig. 6) which is isoteric with CB 1348 which was the most active in a similarly alternating series. It may be no more than a particularly favourable surface activity which enables this particular drug to circulate and penetrate within an organism that endows it with its favourable therapeutic activity, for its chemical reactivity is no different from the other members of the series.

Another group of compounds in which variants of the carrying structure, which have little or no influence on the chemical reactivity of the chloroethylamine group, have been synthesized is the group related to naturally occurring substances. As examples of this type we have

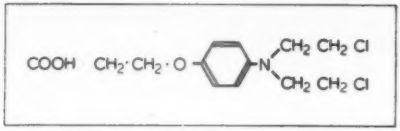


FIG. 6.

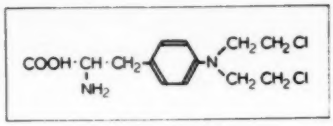


FIG. 7.—CB 3007.

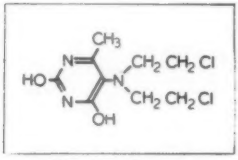


FIG. 8.—Dopan.

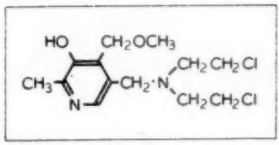


FIG. 9.

dichloroethylaminophenylalanine (Fig. 7) (Bergel and Stock, 1954; Larionov *et al.*, 1955) which is related to the naturally occurring amino acid phenylalanine. A pyrimidine type is exemplified by 2 : 6-dihydroxy-4-methyl-5-di-2′-chloroethylaminopyrimidine (Fig. 8)—known as Dopan (Larionov, 1956). A third example (Fig. 9) is a derivative of pyridoxine carrying a chloroethylamine group (Stock *et al.*, 1951). It is possible that the biological activity of these compounds which is of relatively high order, might be attributable to the incorporation of the whole molecule into a natural metabolic process in which, at first, only the carrying structure is involved and thus the chloroethylamino group is carried into a particularly susceptible part of the organism.

The search for a method by which compounds of this type might be endowed with some level of selectivity led into the interesting field of what we may call "latent activity" types. As we mentioned earlier it is possible to produce an aniline nitrogen mustard (Fig. 2) that is inactive, by introducing electron-attracting substituents, particularly in the *para* position. If such a group could be found which under *in vivo* conditions might be converted to either a neutral or electron-donating group, then it should be possible to synthesize a drug that would be inactive until such a chemical conversion had taken place within the organism. Just such a series are the nitrogen mustards derived from *p*-aminoazobenzene (Fig. 10A)

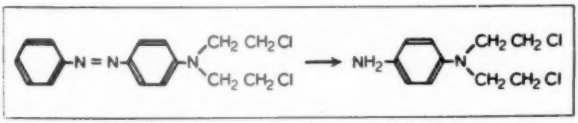


FIG. 10A.

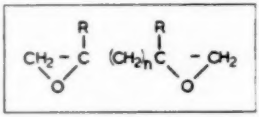


FIG. 10B.

FIG. 11.

(Ross and Warwick, 1956*a*). You will recall that the activity of Prontosil depends on the reduction of the azo group to give the sulphanilamide which is the active bactericide. Similarly the dichloroethylaminoazobenzene which has a hydrolysis rate so low as to ensure inactivity, would yield on the reductive fission of the azo group the highly reactive dichloroethyl derivative of phenylene diamine (Fig. 10B), which is biologically active. The development of this series by the introduction of substituent groups on the benzene rings particularly *ortho* to the azo linkage has produced a number of compounds in which enhanced activity is found in just those drugs where the substituent groupings will tend to assist the ease of fission of the azo linkage. In fact, comparison of the reduction rate of the azo linkage by the xanthine xanthine-oxidase system with biological activity in the series shows a very good correlation between high reduction rate and high biological activity (Ross and Warwick, 1955, 1956*b*).

I want to mention other alkylating agents that have been found to possess similar biological activity. The diepoxides (Fig. 11) are certainly alkylating compounds and capable of reacting with the same sort of active functional groups as the nitrogen mustards (Fraenkel-Conrat, 1944; Ross, 1953). The necessity for two epoxy groups within the molecule is an important link between the two series and gave strength to the early ideas of cross-linking mechanisms being an important part of their mode of action (Goldacre *et al.*, 1949). In this series the substituent groups on the α- and β-carbon atoms which reduce the reactivity of the epoxide ring also reduce biological activity. The most active compound in this series is the shortest molecule, the one derived from butadiene (Fig. 11; n=0). The extending of the inter-epoxy distance by a methylene chain produces compounds of diminishing activity as the methylene chain increases in length.

There is a similar chain-lengthening effect observed in the series of the dimethanesulphonyl esters (Fig. 12) of which Myleran is the best-known member. In this series, the most active compounds are those where the number of methylene units separating the two ester groups is four and five. Below four and above five activity rapidly falls away (Haddow and Timmis, 1953). The alkylating power of the dimethanesulphonyl esters can be altered by substituents on the end groups of the methylene chain, and such changes are accompanied by modification of the biological activity. Changing the methyl radical of the methanesulphonyl group for the *p*-toluyl radical has little effect on the rate of hydrolysis, but the resulting compound is biologically inactive. To refer back for a moment to the nitrogen mustard series, there was a group of compounds synthesized to test the importance of proximity of the two chloroethyl arms in the molecule by making chloroethyl diamines in which the two amino groups, each carrying one chloroethyl arm, could be separated by a

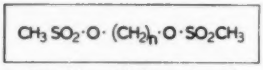


FIG. 12.—Myleran (n=4).

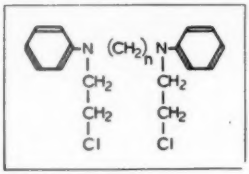


FIG. 13.

variable number of methylene groups (Fig. 13). All these compounds were chemically reactive but biological activity was lost when the methylene chain was increased beyond four units (Kon and Roberts, 1950).

That there should be three different types of alkylating compounds all requiring bifunctionality for anti-tumour activity and all exhibiting this additional structural requirement of an optimum distance between the functional group certainly arouses the sort of speculation that led Ehrlich to propound his theories of the interaction between drug and the organism being affected.

I have done no more than hint at the chemical theories that have been proposed to explain the observed biological activity of this type of compound. Perhaps the most attractive are those which depend on the drug penetrating the nucleus, reacting directly with nucleoprotein and so disturbing the subsequent behaviour of the chromosomes. On the other hand, it may be that alkylation of essential metabolic precursors causes the subsequent aberrations. If this were the case, we should be producing what could best be described as *in vivo* anti-metabolites.

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Dr. A. L. Walpole (Imperial Chemicals (Pharmaceuticals) Ltd.) referred to work with which he had been associated upon the biological effects of a series of alkylating agents rather similar in properties to the nitrogen mustards. With these substances, of which triethylenemelamine (T.E.M.) was the best-known example, activity depended upon the presence in the molecule of one or more ethyleneimino groups. In this series, as with nitrogen mustards and epoxides, tumour-inhibitory activity was in general limited to polyfunctional compounds, i.e. compounds containing more than one reactive or "functional" group in the molecule—here more than one ethyleneimino group. On the other hand he had shown that carcinogenic activity was not so limited. With several monofunctional ethyleneimine derivatives, e.g. N-acetylethyleneimine, subcutaneous

sarcomata were readily induced in rats or mice, although the substances in question were not tumour-inhibitory. Monofunctional ethyleneimines were known, however, which, contrary to the general rule, inhibited the growth of experimental tumours, and exceptions of this kind merited perhaps more attention than they had received. In this connexion the tumour-inhibitory activity of ethyl methanesulphonate ($CH_3SO_2OC_2H_5$), reported by Professor A. Haddow, was of considerable interest.

Referring to the contrast between the dramatic effects of some anti-tumour agents upon experimental tumours and the severe limitations to their usefulness, particularly against solid tumours, in man, Dr. Walpole suggested that it was instructive to envisage three types of selective toxicity, directed respectively towards (*a*) all dividing cells, normal or neoplastic, within the body; (*b*) cells of or arising from one or other tissue; and (*c*) neoplastic cells as such. Available anti-tumour agents, of both the cytotoxic and anti-metabolite class, were possessed in large measure of a selective toxic action of the first type. By virtue of this they inhibited growth of the rapidly growing animal tumours commonly used for "screening" but not that of much slower growing solid neoplasms in man, at levels of dosage below those which produced fatal damage in the more actively proliferating normal tissues, e.g. bone-marrow and intestinal mucosa, of their respective hosts. This was not the whole story, as different agents had, in addition, selective effects of type (*b*). Thus Myleran, for example, was particularly damaging to cells of the myeloid series and particularly effective in myeloid leukæmia. There was, however, no clear evidence of any substance having a toxic action preferentially directed towards neoplastic cells as such.

Professor J. F. Danielli (Department of Zoology, King's College, London) said that it was probable that in very many cases there was no single outstanding chemical difference between malignant cells and other normal cells of the body. If no such single major difference existed, it was necessary to find a chemotherapeutic procedure which could be capable of exploiting small differences between normal and malignant cells. Theoretically this could be done usefully by making the action of a drug depend simultaneously upon several variables. For example, most of the anti-tumour agents which had been developed based on the nitrogen mustards had been thought to owe their effect to their relatively selective activity upon cells which were approaching division. Now if, in addition to dependence upon this difference between tumour and many normal cells, we made activity of the drug dependent also upon enzymic activation of the drug and upon its active transport into a cell, we could expect to obtain much higher selectivity than could possibly be obtained by using only the difference between dividing and non-dividing cells. Preliminary experiments had shown that this procedure could be used in practice (Danielli, 1954; Hebborn and Danielli, 1956).

Professor Haddow had suggested that the most rational approach to tumour therapy would be based upon exploitation of the fundamental differences between a tumour cell and a homologous normal cell. It seemed likely that in many cases this fundamental difference was not primarily biochemical in nature, and that such biochemical differences as existed in many cases were secondary consequences of a more fundamental disturbance. Some light upon what was likely to be involved had recently been obtained by the transplantation of cell nuclei from cell to cell by micromanipulation. These experiments had shown that, whereas a cell nucleus controlled the nature of the macromolecules available to the cell, in many instances the way in which these molecules were built into functional units was determined by the cytoplasm. The cytoplasmic determinants probably owed their specificity more to their organization than to the properties of their constituent macromolecules. In so far as the difference between normal and malignant cells was to be found in a difference between the cytoplasmic determinants, we should have to reach a much deeper understanding of the nature of these determinants before a fundamental therapy would be possible (Danielli *et al.*, 1955).

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Dr. Edith Paterson (Christie Hospital and Holt Radium Institute, Manchester): The large number of closely related cytostatic compounds becoming available for clinical trial requires that the screening on human malignant disease should be as accurate as possible. For example, are there any real differences in effect, or special indications for triethylene melamine compound with triethylene phosphoramide or triethylene thiophosphoramide?

Since the use of ultimate survival times after chemotherapy of patients with malignant disease is not at present a realistic measure, I have used the length of remission after treatment by a given compound compared in the same patient with the remission obtained by one of the more established compounds, such as HN2 in Hodgkin's disease. In this way, the relative values of new compounds can be determined if care is taken that some patients are treated

by the new compound before, and some after, a trial of a more established compound. I use a method of obtaining a "clinical index" for the effects of a compound. This is based on an assessment of the change, beneficial or otherwise, in each presenting symptom at the time of treatment. I feel that this is more accurate and more specific in establishing the clinical effects and, therefore, the relative merits of a new compound, than is a clinical impression. Both methods of assessment should be in general agreement if the basis of the scoring system is sound.

Second Session: Anti-Metabolites

Chairman—Professor F. BERGEL, D. Phil.Nat., Ph.D., D.Sc., F.R.I.C.

Dr. George Bosworth Brown (Sloan-Kettering Institute for Cancer Research, New York): *Structure-Activity Relationships*

The evidence, which has been recently reviewed (Brown, 1954, 1956), that analogues of the larger molecules which can serve as polynucleotide precursors may have a chance of more selectively inhibiting specific tissues was discussed. Some of the biochemical pathways by which purines, nucleosides and nucleotides can be incorporated into the nucleic acids were outlined. The facts which indicate that certain unnatural analogues can be handled by the same enzymes which catalyze some of those reactions were summarized, as was that which suggests that certain anti-metabolites may be incorporated into polynucleotides *in lieu* of the normal components. Particular emphasis was placed upon evidence which suggests that certain inhibitory analogues (notably 2,6-diaminopurine and 9-β-*D*-ribofuranosyl purine) do not exert their anti-metabolite action by incorporation into polynucleotides, but that they may well do so through formation of analogues of ATP or of dinucleotide co-enzymes. Thus there are at least three "targets" for potential anti-metabolites of purine (or pyrimidine) derivatives: the functional, metabolically active, RNA; the DNA of the chromosomes; or those functional co-enzymes which are nucleotide in character.

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Dr. Aaron Bendich (Sloan-Kettering Institute for Cancer Research, New York): *Structure-Activity Relationships*

More than 16,000 compounds and extracts of natural materials which comprise almost the entire gamut of organic chemical types, have to date been tested in the Division of Experimental Chemotherapy of the Sloan-Kettering Institute for possible anti-tumour or anti-leukæmic activity. Percentage-wise, there were more examples of active substances found among derivatives of the nucleic acids than in any other class of substances. Those active purine and pyrimidine derivatives which have been revealed in this way are, unfortunately, few in number. Other anti-tumour agents such as the anti-folics or azaserine, &c., have been found to interfere with the biogenesis of purines either for nucleic acid or for purine co-enzyme biosynthesis. These various compounds therefore appear to have nucleic acids or the purine-containing co-enzymes or ATP as their target and our programme of synthesis of anti-tumour agents has been designed with these factors in mind.

There are certain principles which, at least in part, have guided us in our synthetic efforts. These have been based on the few purine and pyrimidine derivatives which have proved to possess either an anti-tumour activity or were found to behave as anti-metabolites. Adenine (6-aminopurine) and guanine (2-amino-6-hydroxypurine) occur in all nucleic acids which have been examined and these are also components of various co-enzymes and of ATP. Very recently another purine has been isolated from deoxyribonucleic acids (DNA). This derivative of adenine is 6-methylaminopurine. Another compound of importance is hypoxanthine (6-hydroxypurine) and this, in the form of its 9-β-*D*-ribofuranosyl-5′-phosphate, occupies a central position in the biosynthesis of the naturally occurring purines. Among the purine derivatives which have shown an anti-tumour activity are 6-mercapto, 6-chloro, 2,6-diaminopurine, the parent, purine, itself and 8-azaguanine. In each of these cases, there is a single structural alteration when their structures are compared with the purines adenine, guanine or hypoxanthine. Thus, for example, 6-mercaptopurine may be considered as a simple derivative of either adenine or hypoxanthine involving just a single change in structure at position 6 of the purine nucleus. The same can be said for 2,6-diaminopurine. The latter compound can be considered to be an analogue of adenine in which the hydrogen at position 2 has been replaced by an amino group or, alternatively, as an analogue of guanine in which the 6-hydroxyl of guanine has been replaced by an amino group. Similarly, 6-chloropurine or purine itself may be visualized as a structural analogue of adenine involving a single structural alteration. Replacement of carbon No. 8 of guanine by nitrogen affords the compound 8-azaguanine. Whereas these analogues show an activity

against one or another rat or mouse tumour, only 6-mercapto- and 6-chloropurine have shown a clinical interest.

However, a second structural change in the active purine derivatives yields compounds which are inactive as anti-tumour agents. For example, 8-azapurine or 8-aza-6-mercaptopurine are quite inactive in this regard. These structural relationships constitute the basis of some of the principles which have guided us in our synthetic experiments in the purine and pyrimidine series and in the nucleoside derivatives as well.

It would probably be a serious error if we were very rigid in our ideas in this field. These active compounds, although very encouraging, are very few in number, and may be too few from which to draw hard and fast rules. Furthermore, we know very little as to the actual mechanism of their action. Hence, we should not rule out other possibilities even though they may violate our tentative guiding principles. One example of this is the compound 6-methylpurine which is one of the most toxic agents which has been studied in the Chemotherapy Division. It was thought that the 6-trifluoromethyl analogue (that is, the compound in which fluorine atoms have replaced all three hydrogen atoms of the methyl group in the 6-methylpurine) might be of interest. Although this new compound has turned out to be quite interesting from the pure chemical and physico-chemical standpoint, it was found to be non-toxic to animals at dose levels several hundred times larger than those of 6-methylpurine.

We must also not lose sight of the fact that a number of anti-tumour agents have resulted from a purely empirical testing approach. As we study the meagre fruits of the empirical testing programme, certain guiding principles emerge, one of which I have just mentioned. We should like to think that an exploitation of these principles might be characterized as an enlightened empiricism but it is quite clear that new principles have yet to be discovered. Although the nucleic acids and the purine co-enzymes still appear to be a very fruitful target for the chemotherapist, he should not shut his eyes to other possibilities because of preconceived notions.

Dr. Gertrude B. Elion (Wellcome Research Laboratories, Tuckahoe, New York): *Structure-Activity Relationships*

The optimal differential toxicity (therapeutic index) in a series of biologically active materials often depends on details of fine chemical structure in a manner which is revealed only by the preparation and testing of a series of related substances. Among substances which have anti-tumour activity the overall differential effect is often small and the chemical-biological patterns which emerge from such studies are often rudimentary as a result. On the whole such investigations tend to reveal chemical variations which result in inactivity rather than to suggest a series of chemical alterations in an active molecule which may lead to progressive improvements in therapeutic index. Nevertheless, the biochemist is an optimist and is never truly satisfied until he has explored a hundred or more variations for himself. I shall not discuss all of these variations but only indicate what effect some of the alterations in chemical structure have had on the activity of 6-mercaptopurine against sarcoma 180.

We are indebted for the tumour data to Drs. C. C. Stock and D. A. Clarke of the Chemotherapy Division of the Sloan-Kettering Institute. In Tables I and II the doses given are, in general, the maximum tolerated doses of the compounds.

Alkylation of any of the purine ring nitrogens led to a diminution or abolition of the anti-tumour effect of 6-mercaptopurine (Table I). Only the 1-methyl derivative retained any activity and this was of a borderline variety. In all cases, toxicity was decreased.

Introduction of other groups, e.g. SH, OH, CH_3, at positions 2 or 8 of the purine ring led, in general, to a reduction in toxicity and a loss of biological activity. This was not the case, however, for the 2-amino derivative. Thioguanine is about ten times as active as 6-mercaptopurine on sarcoma 180 as well as against adenocarcinoma 755 in our laboratory. However, this compound is also ten times as toxic for most experimental animals. In clinical trials thioguanine is only a little more active than 6-mercaptopurine and several times as difficult to make. An attempt to improve the chemotherapeutic index of thioguanine by substitutions of the amino hydrogens by alkyl or aryl groups led only to diminished activity (e.g. 2-CH_3NH), or to inactivity.

Substitution on the sulphur has produced, on the whole, less toxic compounds and some of these have retained considerable activity, particularly the methylmercapto and benzylmercapto compounds. A number of benzylmercaptopurines with various substituents in the benzene nucleus have been less active. The 6-methylmercaptopurine is now undergoing clinical trial.

An exploration of substituents other than sulphur on the 6-position (Table II) has thus far proved somewhat disappointing. The 6-methyl compound is very toxic but appears to have very little effect on the tumour size. Both the 6-bromo and 6-methylamino compounds show borderline activity. In this connexion it should be mentioned that 6-chloropurine has

been reported to be active on sarcoma 180 at doses of 500 mg./kg. Although the 6-CN and 6-COOH purines are inactive, compounds derived from these are being prepared and tested.

The relationship between structure and activity is actually more complicated than these results would indicate. The data presented have been for tumour inhibition in the usual eight-day period. However, tumour regression rate may be far more important. Tests for this type of activity have now been carried out and with one or two compounds the results are particularly striking. Thus purine-6-thioglucoside produces scarcely any inhibition of tumour growth in eight days at a dosage schedule which causes almost 100% regressions on longer holding. This compound is now entering clinical trial and it remains to be seen whether this type of effect on animal tumours has any relationship to clinical effectiveness.

TABLE I.—EFFECTS OF 6-MERCAPTOPURINE DERIVATIVES ON SARCOMA 180

Purine	Dose mg./kg.	Diameter Index*	Purine	Dose mg./kg.	Diameter Index*
6-SH	25	0·64	2-CH_3-6-SH	125	1·3
6-SH	100	0·48	2-NH_2-6-SH	5	0·48
1-CH_3-6-SH	250	0·76	2-CH_3NH-6-SH	200	0·56
3-CH_3-6-SH	125	0·97	2-$(CH_3)_2N$-6-SH	500	1·21
7-CH_3-6-SH	300	1·0	2-C_2H_5NH-6-SH	50	1·16
9-$C_6H_5CH_2$-6-SH	125	0·97	2-C_6H_5NH-6-SH	500	0·85
6,8-$(SH)_2$	65	0·85	6-CH_3S	500	0·67
6-SH-8-OH	600	0·91	6-C_2H_5S	125	0·95
6-SH-8-CH_3	200	0·93	6-$C_6H_5CH_2S$	250	0·63
2,6-$(SH)_2$	750	0·85	6-C_6H_5S	500	0·99
2-OH-6-SH	200	0·87	6-SCH_2COOH	500	0·71

*Ratio of average treated tumour diameter to control tumour diameter.

TABLE II.—EFFECTS OF SOME 6-SUBSTITUTED PURINES ON SARCOMA 180.

6-R-Purine	Dose mg./kg.	Diameter Index	6-R-Purine	Dose mg./kg.	Diameter Index
$NHNH_2$	50	0·96	$N(CH_3)_2$	50	0·90
CH_3	3	0·88	Br	125	0·78
OCH_3	750	0·92	CN	250	0·93
$NHCH_3$	75	0·78	COOH	125	0·88

Mr. G. M. Timmis (Chester Beatty Research Institute): *New Anti-folic Acids and Anti-purines*

Although the treatment of malignant disease with drugs having anti-folic acid activity has not been discussed here, these drugs are valuable in the treatment of acute leukæmia and have also produced some improvement in cases of breast cancer (Colsky, 1954) and in rhabdomyosarcomas (Colsky, 1954; Farber, 1954). That the drug action against leukæmia is at least closely related to an anti-metabolite effect, is indicated by the prevention of the normal effect of Methotrexate on a mouse leukæmia, by the administration of folic acid (Burchenal *et al.*, 1949). I would therefore like to mention very briefly the results of a recent investigation into anti-folic drugs (Felton and Timmis, 1955; Timmis *et al.*, 1957) wherein we have abandoned the sort of close structural analogy which relates, e.g., Methotrexate to folic acid, in favour of simpler structures (I and II, Fig. 1). The effect of compounds of these series on *Str. fæcalis* has been examined by Dr. H. O. J. Collier and Miss P. Huskinson and fairly marked anti-folic acid activity has been found in some cases; e.g. I, X=Y=NH_2, Z=4′-chloro- and II, X=Y=NH_2, Z=4′-chloro-, both give inhibition coefficients of about 90; still higher activities appear, when the benzene ring is replaced by naphthalene. Both X and Y must usually represent NH_2 groups before high activity is attained.

One reason for trying structure I was a degree of spatial resemblance to the simple pteridine structure (the ring-system of folic acid). Substances of structure II were initially made and tested because the facile *in vitro* oxidation of type I to type II indicated the possibility of a similar transformation *in vivo*. Although several anti-folics of high potency have been found amongst substances of type II the available evidence argues against the activity of type I being dependent upon an initial conversion of I to II (Fig. 1).

Some new types of purine analogues with anti-purine activity (described at the Ciba Symposium on the Chemistry and Biology of Purines, May 8–10, 1956) may also be mentioned.

Purine itself and certain simple derivatives such as 6-methyl- and 6-chloropurine are anti-purines (anti-adenine or anti-guanine) but exhibit, both clinically and in experimental animals, toxic side-effects. Furthermore, Dr. George B. Brown has shown that the attachment of a ribose moiety to purine or 6-methylpurine considerably enhances the toxicity. Since it has been established that the ribose moiety is attached to a precursor of purine in the biosynthesis of nucleic acid and remains attached throughout the nucleotide and nucleoside stages, a sugar residue had appeared to be a suitable residue to attach to a simple purine analogue. The possibility, however, of toxicity being thereby enhanced led us to

I

II

ANTI-FOLIC ACTIVITY

X	Y	Z	Approximate Inhibition Factor
NMe_2	NH_2	4'-Cl	5,800
NH_2	NH_2	H	160
NH_2	NH_2	4'-Cl	90
NH_2	NH_2	3'-Cl	89
NH_2	NH_2	2'-Cl	95
OH	NH_2	4'-Cl	92
OH	H	4'-Cl	10,000*
OH	OH	4'-Cl	> 50,000
NH_2	H	4'-Cl	> 50,000
NH_2	NH_2	$4'-NO_2$	> 50,000

*Not fully competitive

FIG. 1.

ANTI-FOLIC ACID ACTIVITY

X	Y	Z	Inhibition Factor (approx.)	Approx. Inhibition Factor of related Aso-compound
NH_2	NH_2	H	527	160
NH_2	NH_2	4'-Cl	72	90
NH_2	NH_2	3'-Cl	395	89
NH_2	NH_2	2'-Cl	165	95
NMe_2	NH_2	4'-Cl	> 50,000	5,800
NH_2	NH_2	4'-Cl	> 50,000	92
OH	H	4'-Cl	> 50,000	10,000
SH	H	4'-Cl	> 50,000	—
NH_2	H	4'-Cl	> 50,000	> 50,000

III

IV

V

VI

R = CH_3, H

FIG. 2.

attach other, somewhat analogous, cyclic substituents instead of the sugar. Of the purine and 8-azapurines so far made, III, IV, V and VI (Fig. 2) have been found, by Dr. H. O. J. Collier and Miss P. Huskinson, to be anti-guanines of more or less activity. III is the most active in this respect having about three times the activity of 6-mercaptopurine.

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Dr. D. A. G. Galton (Chester Beatty Research Institute): *Clinical and Biological Aspects*

I propose briefly to consider, first, the relation between animal and human malignant disease in their response to therapeutic trials; second, the similarities and differences between cytostatic drugs and anti-metabolites from the clinical viewpoint; lastly I shall sketch in outline the therapeutic use of the main groups of anti-metabolites, especially in acute leukæmia.

A disturbing feature in the work of testing compounds for anti-tumour activity is that so many compounds are effective in laboratory animals but are without effect in a majority of human neoplasms. Dr. Walpole has discussed this matter and I endorse his views. The range of sensitivity in human malignant disease is narrow. With rare exceptions carcinomas are resistant to chemotherapy, as are malignant tumours arising in bone, connective tissue and the central nervous system. The only conditions that respond with any regularity to chemotherapy are the malignant lymphomas and leukæmias, and, less commonly, the even rarer neuroblastomas and rhabdomyosarcomas. The sensitive conditions differ in two respects from the resistant neoplasms. First, they are often generalized diseases involving comparatively large masses of abnormal tissue in relation to total body-weight: secondly the abnormal tissue often contains a high proportion of rapidly dividing cells. As a result of either or both of these circumstances the total nutritional requirements and metabolic turnover of these growths is substantial in proportion to the metabolic activities of the whole body. In contrast, carcinomas, although we usually think of them as rapidly growing, often grow surprisingly slowly, contain a very small proportion of actively dividing cells, and weigh very little in relation to total body-weight. Much of the metabolic activity of human carcinomas is concerned not only with increasing the bulk of the tumour but in efforts at differentiation which involve attempts at synthesizing substances like mucin or keratin. Now the common laboratory tumours of small animals, usually mice and rats, are frequently as large as or larger than the animals themselves. They are mostly undifferentiated growths containing a high proportion of rapidly dividing cells, and their growth rate is rapid compared with that of the host. A greater proportion of a given dose of the compound on trial is therefore likely to find its way to these animal tumours than in most human carcinomas where the amount likely to reach the growth must be infinitesimal. In the case of cytostatic drugs whose distribution throughout the body appears to be entirely random, the tumour is as likely as any other tissue to receive its share, but in the case of an anti-metabolite it will receive proportionately less than the rest of the body unless the tumour is very large or unless the metabolic process in question is so much more rapid in the tumour that the substance is selectively taken up by it, as the thyroid takes up iodine.

The poor vascularity of human carcinomas was often quoted as a major obstacle by those who saw no future in tumour chemotherapy. Tumours were known to be often largely necrotic and it was thought that no drug would ever reach the viable portions. In fact, carcinomas always receive enough blood to enable them to survive and to metastasize even though the survival of any particular mass is precarious. It is now an everyday occurrence to see widespread and bulky metastases from mammary carcinomas undergoing rapid regression during treatment with sex hormones. It is therefore likely that if the right compound were available it would reach the most remote growths following systemic administration. The possibility of obtaining selective uptake will depend on finding a difference between tumour behaviour and that of the rest of the body. No qualitative peculiarities of malignant growth have been demonstrated so quantitative differences will have to be exploited. It is in this respect that the study of antimetabolites would appear to offer better prospects than that of cytostatic agents.

Three groups of anti-metabolites have been tried clinically: they are antagonists of folic acid, of purines, and of amino acids. All are ineffective in the treatment of carcinomas but have been of some value in neuroblastomas, rhabdomyosarcomas and occasionally in reticulosarcomas. They are chiefly of value in the treatment of acute leukæmia for which they have now become the standard form of therapy.

In comparing anti-metabolites as a class with cytostatic drugs we find little overlap in their clinical activity. Some cytostatic drugs have limited efficacy in generalized mammary, ovarian and testicular carcinomas and their range of usefulness in lymphomas is greater than is the case with anti-metabolites. If we consider the leukæmias alone the two groups are again distinct. Thus, cytostatic agents are of little value in acute leukæmias but are really useful in the treatment of chronic leukæmias. Folic acid antagonists are useless in chronic leukæmias but induce remissions in about two-thirds of the cases of acute leukæmia in children; anti-purines are effective in acute leukæmia at all ages and have been used successfully in chronic myeloid but not in chronic lymphatic leukæmia. In acute leukæmia the folic acid antagonists act rapidly, the anti-purines more slowly. With both groups of drugs the bone-marrow must be rendered aplastic before regeneration of normal elements begins. Remission is often in progress two weeks after starting therapy with folic acid antagonists but may be delayed for eight to ten weeks when anti-purines are used.

Cytostatic drugs and anti-metabolites share the serious disadvantages that their beneficial effects always prove to be temporary in every condition in which they are used. In acute leukæmia especially, patients in remission often appear to be healthy in all respects, yet relapse is inevitable. Subsequent remissions may sometimes be obtained by repeating treatment but drug-resistance eventually blocks further therapeutic attempts. There is no cross-resistance between the major groups of chemotherapeutic agents which may therefore be employed successively but a patient who has become resistant to a particular drug will not usually respond to another member of the same group. In acute leukæmia folic acid antagonists, anti-purines, and corticotrophin or steroid hormones may all help to control the disease. In practice it is very difficult to know what to do once remission has been induced by a particular drug. The alternatives are to stop treatment and wait for relapse, and to give maintenance doses in the hope of averting relapse. A third possibility is to combine two drugs acting in different ways, a method which on theoretical grounds might be expected to delay the development of resistance, provided the patient is sensitive to both drugs (Boyland, 1956). Burchenal (1956) has treated a number of children with continuous administration for many months of full doses of 6-mercaptopurine simultaneously with small doses of azaserine. Remissions were maintained for rather longer than is usual when 6-mercaptopurine is used alone.

With new drugs of all kinds toxicity is often a major problem and cannot be predicted from the results in other species. The earlier cytostatic drugs submitted for clinical trial were often so toxic that the more pessimistic of us wondered whether the separation of therapeutic and toxic effects would ever be accomplished. The newer compounds including Myleran, thio-TEPA, CB 1348 and Colcemid are less difficult to handle. Most anti-metabolites have so far proved to be highly toxic but their effects, unlike those of cytostatic drugs, can sometimes be reversed by giving the specific metabolite against which they are acting.

Anti-metabolites, like many cytostatic drugs, frequently affect the gastro-intestinal tract, and some members of all groups induce nausea, vomiting, abdominal cramps and diarrhœa. But there are remarkable differences between individual compounds in each group. Amethopterin, the most useful member of the 4-amino-substituted folic acid antagonists in the treatment of acute leukæmia in children, causes bone-marrow depression, megaloblastosis, ulceration of buccal mucosa, gums, tongue, and later, diarrhœa. These effects can be reversed by citrovorum factor. An analogue of the anti-malarial Daraprim 2,4, diamino, 3-4,dichlorophenyl, 6-methylpyrimidine (Hitchings *et al.*, 1952) is also a folic acid antagonist which has been tried by Dr. Burchenal's group at Memorial Centre with some success in acute leukæmia. But it is very toxic, and like amethopterin causes bone-marrow depression with megaloblastic change, and diarrhœa. Buccal ulceration comes on much later than with amethopterin and nearly half the patients develop generalized skin rashes. In spite of these differences the toxic effects are also reversible by citrovorum factor (Murphy *et al.*, 1954).

The anti-purines show similar diversity in incidence of therapeutic efficacy and of toxic effects, and the relation between the two is just as difficult to explain. 6-mercaptopurine is the most useful drug clinically in acute leukæmia because it is practically non-toxic in therapeutically effective doses. Most other anti-purines are toxic in therapeutic doses. *Purine* itself (Philips *et al.*, 1954) is interesting because it is the only member of the group that damages lymphoid tissue. But clinically it causes VIII nerve deafness, generalized bullous erythema and loss of hair (Burchenal, 1956). *Puromycin amino-nucleoside*, a substance of antibiotic origin, has anti-purine activity but is not useful clinically because it damages the renal tubules with resulting gross albuminuria (Burchenal, 1956). It is clear that in calling these substances anti-purines we are selecting only one of several biological activities, and we may wonder whether it is the anti-purine activity that is responsible for the anti-leukæmic effects. Earlier, I noted the discrepancies between human and animal tumours in their response to chemotherapy. Human and animal leukæmias are also very different. Azaserine (Bartz *et al.*, 1954) for example, though very active against animal leukæmias proved disappointing when tried clinically (Ellison *et al.*, 1954). Even the

relative toxicities of compounds show surprising species differences. Thioguanine (Elion *et al.*, 1952) is twenty times as toxic as 6-mercaptopurine in dogs but the effective dose in humans is about the same for both drugs.

Both of the amino acid antagonists that have been tried clinically are very toxic. Ethionine, an analogue of methionine caused toxic psychosis and damage to liver, skin and gastro-intestinal tract (White and Shimkin, 1954). Selenium cystine (Weisberger and Suhrland, 1956), possibly acting as a cystine antagonist, caused severe nausea and vomiting, epilation, and separation of the nails from their beds. Selenium cystine is of particular interest because it is taken up more readily by leukæmic than by normal granulocytes (Weisberger *et al.*, 1956). Because of its toxicity it will probably be of little value in the treatment of leukæmia but this type of selective action may well prove to be the essential basis of the future therapeutic application of anti-metabolites.

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Dr. F. G. J. Hayhoe (Department of Medicine, University of Cambridge): I fear that those of us who are working in this field, particularly in the chemical and experimental side, may be inclined to over-optimism, and I am not sure that some of the large-scale operations are not open to criticism. Dr. Bendich has told us, for example, that over 16,000 compounds have been obtained by synthesis or other means and investigated to determine their possible activity as purine anti-metabolites in the unit with which he is associated. This is an impressive number of compounds and speaks very highly for the imagination and technical ingenuity of the organic chemists, but it seems the reverse of complimentary to the medical and biological direction which should be guiding the search, since from these 16,000 compounds only one purine antagonist, 6-mercaptopurine, has proved sufficiently valuable to find a place in clinical practice. It is true that a number of other substances do manifest some anti-tumour activity and a few have found a place in clinical experimental trials, but the overall increase in our therapeutic armamentarium derived from this enormous programme of anti-purine synthesis has been very small indeed. Speaking from the point of view of a clinician I should not wish to appear ungrateful for even one active compound, and perhaps 6-mercaptopurine may be regarded as justifying a very great deal of time and energy in synthetic research, but the criticism is difficult to avoid that a very blunderbuss method of obtaining compounds of clinical value is being pursued. Perhaps the extensive researches which are being currently carried out on the intricacies of normal and neoplastic cell nucleoproteins may provide a more satisfactory lead in this matter.

A point of some clinical importance to which Dr. Galton has already referred, and which may one day be provided with a biochemical explanation, is the difference in reaction to certain anti-metabolites, in particular the folic acid antagonists, shown by children as contrasted with adults. Possibly more concentration on clinical and biological phenomena of this kind might have something to contribute to the study of cell sensitivity and resistance to anti-metabolites.

Dr. R. L. Worrall: It is not correct to state that there is no qualitative difference between cancer tissue and normal tissue. The report of a polarographic study by Carruthers and Suntzeff states that the fat of epidermal cancer tissue of mice is qualitatively different from the fat of normal mouse epidermis. Jean Verne reported autoxidation of liver fat in tumour-bearing rats, and the decrease of marrow fat in myeloid leukæmia may be due to this abnormal oxidative process. It is possible, moreover, that leukæmic cells assimilate autoxidizing marrow fat. It is commonly supposed that marrow fat decreases in myeloid leukæmia through normal processes of fat mobilization, but this is a pure assumption, not always recognized as such.

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Section of Anæsthetics

President—KATHARINE G. LLOYD-WILLIAMS, C.B.E., M.D., F.F.A.R.C.S.

[*November* 2, 1956]

The Anæsthetist's Role in Undergraduate Training [*Abridged*]

PRESIDENT'S ADDRESS

By KATHARINE G. LLOYD-WILLIAMS, C.B.E., M.D., F.F.A.R.C.S.

IT is sometimes said that anæsthetics should be a post-graduate subject, some anæsthetists holding the view that it is waste of time for the students and bad for the patients to encourage undergraduates to give anæsthetics at all. This is an extreme view and one with which I heartily disagree, but there is a good deal of variation in the extent of undergraduate teaching in the different schools.

It is not difficult to get enthusiasm from students for such a specialty as anæsthesia. The administration of anæsthetics is essentially practical and almost every student likes to feel he is actually doing something. If he can be given the feeling that he is responsible for the patient, this again enhances his pleasure. Some thirty years of teaching anæsthetics has shown me that one can only expect to drive into the average student a few fundamental facts. Those who wish to reform medical education—and they are many—constantly say that all the students should be taught are the basic principles. This is unfortunately more easily said than done. It is only when one looks back over years of training and practice that one begins to be selective enough to see what *are* the basic principles. The first practical fact I think a student should learn is that from the moment he begins an anæsthetic, he is absolutely responsible for that patient until he regains control of his own airway and is breathing normally. In no other specialty to quite the same extent does a doctor hold the life of the patient in his hands. This cannot be reiterated too often. Though the anæsthetist does, in fact, depute his responsibilities to the sister or nurse in charge who is going to watch the patient recover in bed, he has no right to do so—and certainly would be very foolish to do so—*unless* he is satisfied that he is handing over his patient to a responsible deputy, that the patient is breathing normally, preferably with an airway, that he is a good colour, and has a satisfactory pulse and blood pressure. If the hospital or nursing home is a new one to him he should satisfy himself before he leaves the building that the patient is being satisfactorily watched and cared for. That this is not always done is manifest from reports of unfortunate accidents which appear from time to time in the Press.

The sense of responsibility can be impressed on the student by making him turn on the gas and oxygen machine himself, checking all cylinders, the bottles and their contents. In spite of the convenience of piped oxygen and nitrous oxide to operating theatres, I am very much averse to this system in theatres where undergraduates are being taught. To my mind it is totally wrong to encourage them to think that the responsibility for gases lies in the hands of porters or theatre orderlies outside the theatre. With the introduction of standard colours for cylinders, and non-interchangeable couplings for N_2O and O_2, risk of administering wrong gases is greatly reduced. The same applies to the checking of ampoules. One cannot impress it often enough on the administrator that what he draws up, mixes and injects is entirely his responsibility and that he cannot lay the blame for wrong injections on the sister, nurses or anyone else in the theatre. The standardization of colours for the cylinders, the non-interchangeable coupling, the new methods of marking ampoules to obviate mistakes, all help to make for safety for the patient but *nothing* takes the place of checking the cylinders and checking the ampoules.

Nothing makes me more angry than seeing a student take up a syringe of some fluid, possibly mixed by the resident, and prepare to give it to the patient. When you ask him what he is giving he has not an idea. I should like to emphasize the

importance of teaching students some simple method of local anæsthesia, ensuring that they know the strength of the drugs they wish to use and also the maximum therapeutic dose. Junior house-officers have in some hospitals refused to give anæsthetics because they are too frightened to do so. This is surely a condemnation of our teaching schools. I take the view that a qualified practitioner should be capable of administering some simple form of anæsthetic, both local and general, just as he is expected to remove a toe-nail, open an abscess, do a lumbar puncture or any other simple operative procedure. We cannot after all have specialists performing all the minor operations. But if we expect them to do these things, we must give them a basic training in really simple methods.

My own practice, horrifying as it may appear to some, is to teach undergraduates in the minor operation theatre to anæsthetize the patients with ethyl chloride and ether on a mask to the first plane of the third stage in the anæsthetic room, then to continue with gas and oxygen and ether from a standard machine in the operating theatre. The patients who are reasonably healthy and are not being treated as in-patients are given atropine pre-operatively and walk into the anæsthetic room. They are kept post-operatively in an out-patient ward for a few hours before going home. These out-patient sessions provide one of the best methods for teaching the undergraduate simple methods for the kind of small operation for which in the ordinary way a skilled anæsthetist is not called. As I grow older I find my teaching reduced to a few simple aphorisms, such as, "Keep the patient breathing, and keep the patient pink." Ether has sometimes been called a foolproof anæsthetic. If you give too much ether the patient stops breathing; fortunately with the heart and circulation still in a reasonable state. If you let a patient get blue you can let him die from anoxia at any stage whether under light or deep anæsthesia. The patient gets blue most commonly from obstruction of the airway. It should be reasonably easy to keep a clear airway but all teachers will know how students can hold a patient in such a way and with such good intentions that they successfully prevent the patient from taking a breath at all. Maintaining a clear airway is therefore one of the basic things that can most easily be taught in these sessions.

How to deal with the vomiting patient is also a salutary if disagreeable exercise. When the student has been helped with a case or two, it is possible to let him start on his own and only help him out of his difficulties when they arise. We must all have been shaken by the reports published this year of the number of patients who die as the result of inhaling vomit. I suggest very seriously that some of these patients might have been saved, not by the use of suckers, bronchoscopes or any elaborate procedure at all but by the simple knowledge of how to deal with a patient who is vomiting, by tilting him into the safest position, on his side and maintaining an airway. Here again ether, as a means of anæsthesia by the inexperienced administrator has great advantages over more elegant methods, in that fortunately the patient usually vomits at a stage at which he can still protect himself. His pharyngeal reflexes are still present and all that is needed is to put him into a position head downwards and preferably on his side, possibly with a pillow under his shoulders so that he is not likely to inhale vomit but will cough it up. The same position should be adopted when the patient is removed from the operating table to the trolley after minor operations. In the bad old days every nurse learnt how to deal in a simple way with a vomiting patient. To-day when on the whole patients seldom vomit after modern anæsthetics this complication, when it occurs, is often very badly dealt with.

My third aphorism is: "If a patient will retain an airway under ether anæsthesia he must have lost his pharyngeal reflexes and is therefore in the third stage, i.e. surgical anæsthesia."

If one can get a student to learn these three facts it will give him some confidence when called upon to give a simple anæsthetic i.e. (1) Keep the patient breathing. (2) Keep him pink. (3) If he will retain an airway he must be at any rate in the first plane of the third stage of anæsthesia.

I doubt if you can teach him much more in the undergraduate stage, but he has at least some basis to build on. The use of the gas and oxygen machine in the minor operating theatre is again good practice, though if the administrator is inexperienced it is infinitely safer to use ether on a mask than run any risks of giving an inadequate supply of oxygen to a patient.

Dental anæsthetics.—It is still very common practice for dental surgeons to ask the local general practitioner to give dental gases especially to their own patients. I have recently been sent the results of a questionnaire sent out by the British Medical Students' Association enquiring about the amount of instruction which undergraduates get in giving dental anæsthetics. There are many dentists who are certainly better able to give anæsthetics than the doctor and they sometimes complain that they have to start by teaching their medical colleagues.

This is not surprising when it is realized that some undergraduate schools give no instruction at all in this very important branch of anæsthetics. The possibilities of mishaps occurring in the dental chair are manifold, and every doctor should be aware of them and be given some basic training.

Intravenous injections.—Whether students should be encouraged to give intravenous anæsthetics is perhaps a moot point, but it cannot be denied that the anæsthetist is the best person to teach him to put a needle into a vein. Undergraduates are usually taught by the registrar or house-officer how to take blood for pathological tests during their introductory posts. The patient can be spared much if the anæsthetic staff will spend time on teaching undergraduates how to put a needle into a vein without causing misery to the patient. Which vein to use has been a matter of some controversy. There are some disadvantages in selecting the veins at the elbow. As Professor E. A. Pask has pointed out, there is the risk of damage to the median nerve (or even injection into the ulnar artery) and the veins of the back of the hand have been suggested as the best site. These are not always easy veins for the student to get into because they are more mobile and perivenous injections occur perhaps more frequently but fortunately more obviously. The veins in the ante-cubital fossa are usually better supported by the surrounding tissues and are more easily entered by the inexperienced. The use of veins on the ulnar side of the ante-cubital fossa for injection should never, however tempting, be taught to undergraduates. With the use of an eccentric nozzle on the syringe and the syringe resting on the arm, and with a definite routine for injection, the procedure can be acquired fairly quickly. There is a lot to be said for using the bevel of the needle facing downwards when teaching students (Fig. 1). If after entering the vein they let the needle

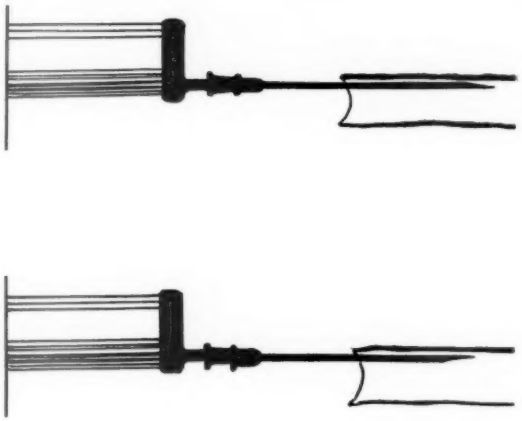


FIG. 1.

"ride up" as is a good precaution, the contents of the syringe will still enter the vein instead of being occluded by the anterior vein wall if the bevel is uppermost. The dangers and treatment of perivenous injection should naturally be impressed on them.

It is often said that anæsthetics for major operations are unsuitable ones for training students. My own view is that there are very few operations indeed where the student cannot be taught something if the anæsthetist will take the trouble. A physician who is a good teacher can cover a large part of medicine on a single case of diabetes or cerebral hæmorrhage, and there are many comparable ways in which the anæsthetist can also teach if he wants to:

(i) How to give an intravenous injection.

(ii) What premedication the patient has received, with the doses. (It is remarkable how few students ever look at the prescription chart or know what drugs their patients are receiving.)

(iii) How to take and keep a record of the pulse and blood pressure—to give only a few instances which come to mind.

There have been a number of articles written and papers read recently on the subject of medical education. We are all agreed that the content of the present syllabus is grossly overcrowded and that it is impossible for the student to acquire or remember all that is crammed into his years of training. Nevertheless every specialist thinks what he is teaching cannot possibly be cut and the burden increases year by year. I think we must not be too greedy of time in teaching our own specialties; we have a part to play in teaching the fundamentals of medicine.

Professor G. W. Pickering says: "The primary purpose of the undergraduate medical course within the University is to train the student's mind so that he can collect and verify facts concerning health and disease in man, and so that he can form a balanced judgment on issues that affect both individuals and groups."

Anæsthesia as a subject for undergraduates is in fact mainly practical, and it behoves us all to ensure that the simple things we teach them, even if few in number as I think they should be, are well understood.

We have, however, a very definite duty towards the next generation not only to impart the facts of our specialties, but to give them a standard of ethics and that sense of responsibility and membership of a great profession that were handed on to us by our predecessors.

The last few years have brought great changes. We live in an age when recruitment for the profession comes from a pool of talent rather than, as in the past, a pool of privilege, and it must lead to the enrichment of the profession. None the less, a background of privilege could and most frequently did in the past give rise to a sense of responsibility, which we should preserve most jealously for the benefit of all. If we wish to maintain professional standards we must first be quite sure that people realize that these standards exist, and it is the duty of the older members of their profession to reiterate again and again quite explicitly what these ideas and ideals are. For example we have, I think, to make a particular effort to show our students that they must preserve a real sense of individual responsibility for what they do.

If we are to retain our standards as professional people and not merely as civil servants doing a routine job bound by hours, conditions and money, we must preserve our independence of thought and that sense of responsibility which should mark the educated professional man. The anæsthetist is really in a unique position to instil these principles into his students for his dealings with them are mainly as individuals, not as groups. The six years of training which a medical course involves should give us ample time and opportunity to instil into our students those principles which we all wish them to have and we can none of us avoid our responsibilities in this respect. We get our students at the most impressionable age and what our standards are and how we view our responsibilities are inevitably the example they take and follow.

The standards we demand from students are what we shall get. I think perhaps we make a mistake in London and in many of the other Universities, in not making more of a ritual of our qualification as "a doctor with the right to practise". In some Universities the taking of some form of the Hippocratic Oath is made part of their Graduation Ceremony. The words may seem archaic and we perhaps cannot subscribe to it in detail but the spirit of it as a standard of ethics is unchangeable.

Section of Dermatology

President—Louis Forman, M.D., F.R.C.P.

[*October* 18, 1956]

Leg Ulcer and Rheumatoid Arthritis. Three Cases.—F. Ray Bettley, F.R.C.P.

Case I.

History.—A housewife, then aged 28, began to develop rheumatoid arthritis in 1950, two months following an attack of salpingitis which had settled down after treatment with penicillin and sulphonamides. In 1952 she developed a rash on the upper part of the front of her chest, three weeks after starting gold therapy; three weeks later, the rash having subsided, gold injections were re-started and continued for fourteen weeks when they were discontinued owing to the reappearance of the rash. This subsided within two weeks of stopping the injections. In 1954 subcutaneous swellings began to appear on the backs of her elbows. During the period March 1954 to March 1955 she received two courses of bee sting therapy applied to the skin overlying her affected joints. In June 1955 an ulcer began to develop on each ankle and in February 1956 she developed a dry pleurisy lasting one week.

Examination on admission in April 1956 showed her to be thin and crippled with rheumatoid arthritis; many subcutaneous "rheumatoid" nodules were present on the extensor surfaces of her arms and over her scapulæ. There was a clean based ulcer 3 in. by 2¼ in. on the outer side of the left ankle.

The smaller ulcer healed slowly on bed rest and local treatment in seven weeks; the larger ulcer only healed after pinch grafting but twelve weeks later broke down at the same time as a fresh ulcer appeared below the outer side of the left knee.

Investigations.—Urine: a few R.B.C. and W.B.C.; culture sterile. Blood urea 27 mg.%. Urea clearance 50% and 31% of normal. I.V.P. normal. Blood counts showed a persistent hypochromic anæmia. W.B.C. counts normal. Blood for L.E. cells strongly positive. Plasma proteins 7·8 grams%. Albumin 3·5 grams%, globulin 4·3 grams%. Electrophoretic pattern showed a raised gamma and alpha-2 globulin. Blood W.R. negative.

Case II.

History.—A housewife, then aged 51, first developed symptoms of rheumatoid arthritis in 1943. From 1951 to 1954 she was treated with various courses of Butazolidin and gold. In 1953 nodules appeared over her elbows and by early 1955 an ulcer had developed on her left ankle.

Examination on admission in February 1955 showed her to be obese and crippled with rheumatoid arthritis; "rheumatoid" nodules were present on the backs of the arms and hands. An ulcer 4 in. by 2½ in. was present on the outer side of the left ankle and one the size of a shilling on the medial side of the base of the left first toe. Chest X-ray showed an area of segmental collapse at the right base which persisted in spite of active treatment. In May and October she had two attacks of constant lower abdominal pain associated with nausea and vomiting and a temperature of 101° F. on one occasion; apart from slight tenderness no other abnormal findings were made clinically or radiologically. In August she had an attack of loss of consciousness for two minutes. Whilst lying in bed she became cyanosed, there was no clonic phase and she was not incontinent. On recovery she complained of a severe right-sided headache. Heart and C.N.S. subsequently normal, as were the EEG and skull X-ray. No healing at all could be induced in these ulcers in spite of nine months in hospital. Grafting failed as also did local injections of hydrocortisone. Systemic steroid therapy was not given at that time. She was discharged home in December.

In August 1956 the ulcer started to extend and to become more painful. She was readmitted in October for possible systemic steroid treatment. Examination showed little change from the previous findings apart from an increase in the size of the ulcers and one fresh one on the medial side of the right first metacarpophalangeal joint.

Investigations.—Urine: normal. Blood counts showed a constant hypochromic anæmia and leucopenia. Blood for L.E. cells strongly positive on two occasions, and negative on two. A positive finding was not associated with any exacerbation of her condition. Plasma

proteins 7·7 grams%, albumin 3·8 grams%, globulin 3·9 grams%. Electrophoretic stri showed a raised alpha-2 globulin and a slightly raised gamma globulin. W.R. negativ

Addendum.—She began prednisone therapy on 6.10.56, so far with no definite change i the size of the ulcer. A week ago purpuric lesions appeared on her legs. Platelet coun 80,000/c.mm.

Case III.

History.—A man, then aged 45, first developed symptoms of rheumatoid arthritis in 1945. In 1947, nodules were present over the left elbow for six months. At the time he was tol that they were "rheumatoid". Raynaud's phenomenon in the hands and feet began in 1952. In 1953 he had gold dermatitis and in April 1954 an ulcer appeared on the medial side o the right ankle.

Examination on admission in November 1954 showed severe arthritis, dusky erythema and telangiectases at the bases of the finger nails, and a clean based ulcer 1 in. in diameter over the medial side of the right ankle.

The ulcer slowly healed over twelve weeks' treatment in hospital, during which time he received hydrocortisone subcutaneously into the base of the ulcer, 25 mg. twice weekly.

Investigations.—Urine: occasional R.B.C. on admission, subsequent deposits normal. Blood counts normal. Blood for L.E. cells (November 1954) negative; (September 1956) positive. Plasma proteins 6·0 grams%, albumin 3·6 grams%, globulin 2·4 grams%. Electrophoretic pattern showed a raised alpha-2 globulin.

Dr. F. Ray Bettley: I have brought these three cases, which have features in common, as examples of a lesion which I have noticed in the last two years or so—the combination of rheumatoid arthritis with ulceration of the legs or feet. When I asked a rheumatologist about this he was inclined to attribute ulceration to immobility and vascular stasis, but I think this is not an acceptable explanation because the legs do not show any such signs. There are no histories of varicose changes and the legs are not usually œdematous. One of the patients now has a good deal of leg œdema, but she did not have that when the ulcers started. She was resting in bed in the ward for many months and the ulcer slowly enlarged at a time when there was no sign of œdema or of arterial insufficiency.

I am indebted to Dr. W. S. C. Copeman who called my attention to the report by Laine and Vainio (1955) on cases which are evidently of this sort. Laine and Vainio do not mention systemic factors in their cases, but it is most significant that these three patients all have features which we usually regard as those of disseminated lupus erythematosus. I do not wish to make a firm diagnosis of lupus erythematosus in these cases, but rather to indicate that, in addition to chronic arthritis and skin ulceration, there is evidence of profound, if not obvious, systemic upset of the kind that is found in disseminated lupus erythematosus.

Biopsy sections have been examined by Professor R. W. Scarff and Dr. A. C. Thackray, who do not at present wish to draw firm conclusions. In many ways they find the histology compatible with lupus erythematosus but two biopsies showed a palisading of histiocytes more suggestive of rheumatoid arthritis. At all events it seems that the histology confirms that something more than vascular stasis is at work.

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Elephantiasis Nostras.—BRIAN RUSSELL, F.R.C.P.

Miss O. M., aged 43.

History.—1943: Bitten by a puppy on the right side of lower lip. About nine months later a small red swelling appeared at this site. It persisted for a few months. Since 1946: Recurrent attacks of redness and swelling of the right sides of both lips and of the right cheek. In later attacks the swelling extended to the nose, eyelids, forehead and scalp.

1950: Admitted to hospital in a severe attack.

1951: A warty lesion was noted on the under-surface of the right side of the tongue. It was excised. The section revealed tuberculosis of the submucosa.

Physical signs.—Non-pitting œdema of the lower half of the face. Firm, finely nodular and scaly surface of the chin. Macrocheilia. Venous congestion and telangiectasia of cheeks and chin. Vasolability, particularly of lower half of the face. Nasal septum deflected to the left. Right pupil larger than the left; no reaction to light; slow transient reaction to accommodation. Facial redness and swelling increase on excitement; right side of face flushes more but sweats less than left side.

Investigations.—Westergren sedimentation rate: 10 mm. in one hour. Blood: hæmoglobin 92%; white cell count normal; Wassermann reaction negative.

X-rays: Chest: calcified foci in right first interspace and right hilum; no active pulmonary lesion. Cervical spine: no bony lesion. Sinuses: mucosal thickening of antra, left more than right.

Bacteriology: Nose—moderate *Staphylococcus pyogenes.* Throat—profuse *Streptococcus hæmolyticus.*

Biopsy from skin of left side of chin: Chronic granulomatous inflammation consistent with tuberculosis or sarcoid. No acid-fast bacilli seen. Several epithelioid cell and giant cell tubercles in dermis, with slight central necrosis and peripheral lymphocytic infiltration. Birefringent particle visible in one giant cell only.

Mantoux reaction: 1 in 1,000 positive.

Past treatments.—Penicillin; Sulphatriad; T.A.B.; superficial X-rays; potassium iodide; ascorbic acid; calciferol (aggravated); isoniazid (115 grams in six months, ineffective); Aureomycin; "tin, gold and iron" from unregistered practitioner; extraction of second right lower premolar for root abscess.

Still's Disease with Recurrent Ulceration of the Legs.—C. M. RIDLEY, M.R.C.P. (for BRIAN RUSSELL, F.R.C.P.)

H. F., aged 14.

History.—This girl first developed painful swellings of the joints at the end of 1948, and the process continued until about two years ago. Since 1949 she has had ulcers on the legs, appearing between October and May and often not healing until well into the summer. She cannot walk, and spends most of her time sitting in a chair. She has never suffered from chilblains.

General health.—Good.

Past history.—Tuberculous gland on right side of neck removed eight years ago.

On examination.—Thin, intelligent girl. Scar on right side of neck. Small glands in axillæ and groins. Typical deformities of rheumatoid arthritis affecting fingers, wrists, elbows, feet, ankles and knees. Marked wasting of limbs. Hands and feet rather cold, but peripheral pulses palpable.

Skin: On the top of the feet and on the calves from just below the knees are some ulcers in various stages of healing and many scars of previous ulceration. The ulcers are round or oval, well defined and shallow, with bluish œdematous edges.

Investigations.—Chest X-ray normal. E.S.R.: 37 mm. in one hour (Westergren). Hæmoglobin 84%, white blood cells 8,200 per c.mm. (polymorphs 68%, eosinophils 1%, lymphocytes 26%, monocytes 5%). Swab from ulcer: *Staph. pyogenes.* Biopsy (ulcer on right big toe): Inflammatory changes with some free iron.

Comment.—It seems probable that the cause of this girl's ulcers is venostasis in an immobile limb with gross wasting of the muscles.

The following cases were also shown:

Subcorneal Pustular Dermatosis.—Dr. I. B. SNEDDON.

Pseudoxanthoma Elasticum (Giant Cell Reaction Nodules).—Dr. ROBERT WARIN.

(1) **Arthropathic Psoriasis.** (2) **Widespread Morphœa.**—Dr. R. H. MEARA.

Dyselastosis with Cysts and Comedones.—Dr. J. H. ALLISON (for Dr. F. RAY BETTLEY).

Incontinentia Pigmenti in a Baby of 12 Days.—Dr. G. A. BECK.

Bullous Urticaria Pigmentosa in a Baby of 2 Months.—Dr. N. A. THORNE.

Nodular Eruption of Back.—Dr. HAROLD WILSON.

Xeroderma Pigmentosum.—Dr. D. L. REES (for Dr. H. J. WALLACE).

Maculo-anæsthetic Leprosy.—Dr. DAVID ERSKINE.

Congenital Poikiloderma (Thomson).—Dr. J. G. COWLEY (for Dr. F. RAY BETTLEY).

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[*Continued on p. 24*

Section of Endocrinology

President—T. Russell Fraser, M.D., F.R.C.P., D.P.M.

[*October* 24, 1956]

Diagnostic Procedures in Bone Disease [*Abridged*]

By T. Russell Fraser, M.D., F.R.C.P., D.P.M.

(*Department of Medicine, Postgraduate Medical School of London*)

Metabolic bone disease is characteristically generalized as distinct from localized or invasive bone disease. But invasive bone disease, for example myeloma, may become widespread and so simulate a generalized or metabolic disease of bone; and on the other hand osteoporosis, a metabolic disease of bone, may predominantly affect the axial skeleton.

Much of the metabolic disorder of bone can be revealed from the metabolism of calcium and phosphorus; but in the future the metabolism of bone matrix may also provide diagnostic tools. Bone is constantly being deposited, remodelled and resorbed. Body fluids often reflect abnormalities of these processes; more direct measures of the rates of bone deposition give more sensitive reflections of bone metabolism.

The important metabolic bone disorders are those which cause thinning of bone and it is with the diagnosis of these disorders which we shall be concerned: (i) That due to excessive bone resorption, which is typically reflected in hypercalcæmia with hypercalciuria and high serum alkaline phosphatase; low serum phosphate may reflect that hyperparathyroidism is the cause. (ii) That due to defective calcification or rickets or osteomalacia, which is typically reflected in the "low calcifiability serum", i.e. one showing a low calcium x phosphate product along with the probably compensatory high serum alkaline phosphatase. (iii) Insufficient bone formation or osteoporosis, or bone atrophy with which we find normal serum levels of Ca and P and phosphatase.

(i) The Recognition of Excessive Bone Resorption due to Hyperparathyroidism

Gley recognized in 1890 that parathyroidectomy leads to tetany, and in 1909 McCallum and Voegtlin showed its association with low serum calcium and its relief by injected calcium. Following this, Erdheim in Vienna was led to study the parathyroids in cases of bone disease —and so to his discovery of the enlarged parathyroids in osteomalacia, which he correctly regarded as secondary. Later, however, thin bones with osteitis fibrosa were also found in his department to be associated with single parathyroid tumours which were clearly not of secondary origin. And so in 1926 a famous Viennese tram conductor, Albert, who had suffered many pathological fractures, was finally operated upon by Mandel and the offending parathyroid tumour was removed.

This pathological approach to hyperparathyroidism has its present-day counterpart in the recognition of hyperparathyroidism either by X-ray or by bone biopsy, i.e. in its recognition from signs of excessive bone resorption. But unfortunately, the typical pathology is only found in the severer instances of this bone disease. In these cases the excessive bone resorption can usually be recognized from X-rays of hands, where it is shown as subperiosteal erosion. This finding is also seen in uræmic osteodystrophy (secondary hyperparathyroidism) and so is not a hallmark of primary hyperparathyroidism. For this distinction we must

turn to the biochemical approach; as also for the recognition of those cases with less gross bone disease.

Concurrently with these new Viennese pathological approaches to hyperparathyroidism, studies were being made on the calcium metabolism of similar cases in the U.S.A. In 1930, from a blood sample showing hypercalcæmia, Dubois diagnosed hyperparathyroidism in another famous patient with pathological fractures, Captain Martell. Since then, the physicians Aub, Bauer and Albright and others, have studied many patients and defined the biochemical criteria for the diagnosis of hyperparathyroidism, based on the estimation of calcium and phosphorus and phosphatase in serum and urine. These procedures disclose parathyroid tumours not only among patients with bone disease, but even more among patients with renal stones and no bone disease.

In hyperparathyroidism with bone disease but without uræmia, these biochemical findings are typical—the raised serum and urinary calcium, associated with a raised serum alkaline phosphatase and a low serum P. However, only sera with at least two of these abnormalities are diagnostic, i.e. the associated phosphate disorders give the clue. But some cases of hyperparathyroidism do not have bone disease and so have a normal phosphatase, and some others have complicating uræmia so that their serum P is no longer low; fortunately either one or other of these phosphate abnormalities is present in the vast majority. Further, it has emerged over the last decade that several conditions may simulate these biochemical findings of hyperparathyroidism—but not both the Ca and P abnormalities. (*a*) A similar hypercalcæmia may occur in bone invasive disease such as myeloma or secondary carcinomatous involvement of bone; and also in some cases of sarcoidosis and in vitamin D poisoning. (*b*) With chronic uræmia, secondary bone disease compounded of various abnormalities (uræmic osteodystrophy) may occur; usually the absence of hypercalcæmia or hypercalciuria can exclude primary hyperparathyroidism or indeed any cause other than the uræmia. Evidence for these conditions should always be sought in atypical cases. In secondary hyperparathyroidism the serum biochemistry will also reveal signs of the basic cause, i.e. of the uræmia or of the osteomalacia.

An assay of serum or urinary parathormone levels will obviously be a useful diagnostic tool in these atypical cases. At Hammersmith, Davies (1957) has shown that this is possible, on forty-eight-hour urine collections, using a benzoic acid extraction and a mouse-phosphaturia assay procedure.

We have noted that the diagnosis of primary parathyroid overaction is usually clinched by finding abnormal P metabolism in association with hypercalcæmia. It is sometimes useful to exclude the suspicion of hyperparathyroidism by assessing both the serum level and the renal excretion of P. Primary and secondary hyperparathyroidism and also several other conditions, including renal disease and Cushing's syndrome are characterized by a high urinary P excretion. The urinary P excretion can only be assessed in the light of both the serum P level and of the renal glomerular filtration rate. If we estimate the ratio of the renal clearance of P to that of creatinine then we can derive a "phosphate excretion index" (Nordin and Fraser, 1956*a*), which will be high in hyperparathyroidism primary or secondary, as well as in the other conditions noted, and low in hypoparathyroidism. This procedure is useful for the recognition of hypoparathyroidism and for the exclusion of hyperparathyroidism—but when high the index does not help distinguish hyperparathyroidism from the conditions which can simulate it.

(ii) The Recognition of Osteomalacia or Rickets

A firm diagnosis requires the demonstration both of the cause of the osteomalacia and also that the serum has a lowered calcifying power. I shall not discuss the ascertainment of the cause, i.e. the assessment of absorption and also of renal tubular function. In the well-developed cases, the radiological findings alone may be diagnostic—revealing the softness of the bones either by deformities or by Milkman's or partial greenstick-like fractures. In the young there will also be seen the widened translucent metaphysis which is hyperplastic but inadequately calcified.

In the typical case, the biochemical criteria of low calcifiability are found in the serum—a low product of the Ca × P concentrations—together with a high phosphatase level indicative of the hyperplastic osteoid. It is usually the P level which is low, but because of the considerable diurnal and dietary variations in serum P levels this abnormality may not always be recognizable from serum levels alone. For the recognition of doubtful or atypical cases, and for the assessment of cases with a known cause such as steatorrhœa but with no clear evidence of bone involvement, we have two further tests available—the calcium infusion test and the bone biopsy. The osteomalacic bones show an abnormal avidity for intravenous infused Ca. If we exclude the vitamin D-resistant cases, which show a urinary leak for Ca, this can be shown by the low 0–12-hour urinary excretion on the test (Nordin and Fraser, 1956*b*). This test can recognize cases before the serum levels are obviously abnormal. If account is also

taken of the rise in serum levels during the infusion, we can also calculate a four-hour bone retention: which is abnormally high in osteomalacia, including the vitamin D-resistant cases.

Further confirmation can be obtained by iliac crest biopsy. For this procedure it is necessary to prepare undecalcified bone sections so that the abnormally wide osteoid seams may be demonstrated. A final confirmation of the diagnosis of osteomalacia is best obtained by the demonstration of the response to treatment appropriate to the cause discovered—e.g. injected vitamin D in cases of steatorrhœa. If need be in doubtful cases, this may be confirmed by showing the increased retention of calcium by balance studies.

(iii) The Recognition of Osteoporosis

Finally we come to cases with translucent bones without evidence of a primary disorder of Ca metabolism, or of a bone invasive disease. For these cases we reserve the term osteoporosis and the diagnosis at present rests mainly on the exclusion of other disease. It is commonly attributed to defective formation of bone matrix, since what forms is normally calcified; but this basis has not yet been proved or disproved. The radiological diagnosis here consists in the recognition that the bones are abnormally thin. Unfortunately, so much of the "bone density" on an X-ray depends on the soft tissues shadow that variations in body thickness are a large source of error here; and at least about 25% of the body's Ca has to be lost before a recognizable abnormality emerges. There are two tests which may help in the recognition of a metabolic defect in these cases of osteoporosis; the Ca infusion test and the strontium infusion test.

The first test has already been mentioned as useful in the recognition of osteomalacia. The four-hour "bone retention" of Ca on this test tends to be low in osteoporosis (Finlay, Nordin and Fraser, 1956). This first test might be called the early Ca uptake in response to a raised serum Ca level.

In order to observe the bone uptake without raising the serum Ca, we should have to inject a suitable tracer of the Ca atoms and observe their rate of disappearance from the body fluids. For this purpose we have used strontium rather than the possibly dangerous radioactive isotopes and found evidence that it does act as a tracer for Ca in the body. We have given a single intravenous dose of strontium and followed the changing concentrations of strontium in the serum and urine over the subsequent seven days. From this data we have been able to derive the daily uptake of Ca by the bones (Eisenberg, Fraser, Ibbertson and Lowe, 1957).

Interpretation of the curve suggests that there are two main Ca pools in the body. The body-Ca pool, or the exchangeable Ca, comprising not only the Ca in the body fluids but also that on the surface of the bones which appears to exchange freely with the body fluids; and the deeper or deposited bone Ca to which there is a steady deposition and from which there is later a steady resorption. This test measures the size of the first or exchangeable Ca pool—from the extent to which the strontium becomes diluted at the conclusion of mixing. We cannot follow the curves long enough to observe the end of the cycle—the resorption of deposited bone; but the steady rate of strontium disappearance, when corrected for urinary loss, reflects the rate of bone deposition from the exchangeable pool. Abnormal resorption should be revealed on this test by a corresponding abnormality in bone deposition and any imbalance between these processes should be revealed from the Ca balance. Preliminary results show that this dynamic test can more precisely define the disordered Ca metabolism of some bone disorders, than can either estimation of the levels of Ca in the serum and urine or balance studies. Severe thyrotoxicosis shows a depleted Ca pool and a rapid bone turnover; some cases of severe simple osteoporosis show a normal Ca pool but defective bone deposition. Hyperparathyroidism shows both an enlarged exchangeable Ca pool and increased rate of bone turnover.

In conclusion, we see that in severe cases, radiology alone can sometimes define the disorder, and standard biochemical procedures can clinch the diagnosis in these cases. For the diagnosis of hyperparathyroidism or osteomalacia, the estimation of serum and urinary levels of Ca, P and phosphatase can often supply the diagnosis. But hyperparathyroidism without bone disease or with uræmia, may be mimicked by certain other diseases. Infusion tests of Ca and strontium can reveal abnormalities in cases of early osteomalacia and of osteoporosis, though the serum biochemistry may appear normal; these dynamic tests may help to elucidate obscure cases.

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Section of General Practice

President—JOHN H. HUNT, M.A., D.M.

[*October* 17, 1956]

Pædiatrics in General Practice

VALEDICTORY ADDRESS

By GEOFFREY BARBER, O.B.E., M.A., M.B.

INTRODUCTION

PÆDIATRICS is not a special branch of medicine. It is the whole of medicine applied to a special age group. The pædiatrician is just as much a general practitioner of medicine as we are, and we tend to meet him more often than other specialists in domiciliary consultations for several reasons. The main one is that nowadays relatively few children's ailments really need to be treated in hospital provided that home conditions are adequate: because conservative treatment with antibiotics, the greatly improved economic way of life of the majority of people, the freedom from financial commitment especially in domiciliary consultations, the telephone, and the improved home nursing services all make home treatment more possible. And there is a greater realization that it is *preferable* to nurse a child at home, both from the point of view of the danger of further infection developing in hospital where many children are brought together, and from the harm that is done to a young child by separation from its mother and its home, especially when under the age of 5. Experience in children's diseases is one of the most important sides of medical education, and there is no branch of medicine in which the general practitioner can be of more help to the consultant. So many of the symptoms and signs in children's illnesses are transient and rapid, and we see the early stages of illness which may change quite appreciably before we ask his advice; as family doctors we also see a great deal of minor illness which clears up without ever getting to him at all.

That is my subject: illnesses which present the doctor with symptoms or signs which may cause considerable anxiety at the time, and which clear up without any treatment or after-effects, or sometimes without any definite diagnosis.

THE ALIMENTARY SYSTEM

Abdominal symptoms in children equal in number all the other presenting symptoms put together. "Pain in the stomach" occurs with the greatest regularity right from birth; when an infant yells it is for the parent and for the doctor to find out the exact site of the pain. Often an intelligent mother will tell you that the pain does appear "to be in his stomach", and it is one of the nicest points in physical examination for a doctor to decide whether the tenseness of the abdomen is due to the pain or to the child's vocal efforts. It is often very difficult to decide, and can only be done by the most patient and gentle holding of the abdomen, trying to dip through the tension of the recti muscles between the baby's cries. I can never tell this when the baby is lying on its back, and I prefer the mother to nurse it up against her body and for me to slide a hand gently over the baby's stomach in that position. Even when we decide that there is no rigidity in between the yells, it does not tell us that the pain is not in that region, but it does reassure us a little that there is no serious inflammatory invasion of the peritoneal cavity.

I was always taught to listen to the abdomen, whether in a child or an adult. Active peristaltic sounds are reassuring; one of the most sinister pictures is the absolutely silent distended abdomen. So-called obstructive sounds are not always very reliable, although they may give one a guide. A very loud yell is a reassuring sign; for I am more impressed by the child that lies and whimpers pathetically when you touch the abdomen, trying at the same time to push your hands away. It is the picture of an ill child. One has to re-examine these children quite frequently, even at intervals of an hour or so before coming to a decision; this is particularly true of intussusception because it is so difficult to diagnose in the early stages.

The baby and the parent are so intimately bound together that one is always dealing with a parent as well as a child: the parent wants a diagnosis, the child wants relief. It is very often easier to give the former than the latter: and it is for this reason that there are so many labels which we pin on to the infant for the parent's satisfaction. It doesn't even need a doctor to say "wind" and I suppose that a child who has to suck too greedily because of his hunger at too small a teat often does finally blow himself up with air and have a certain amount of difficulty in getting rid of it, but in my experience a child brings up wind extremely easily when he has merely swallowed it, and usually produces his eructation with a certain

amount of liquid accompaniment or possetting and with an extraordinary show of pleasur . Painful wind often seems to be accompanied by an abnormal spasm, and I suspect that a mi d degree of pylorospasm is far commoner in infants during the first few months of their li e than is generally supposed, and that some of the pain which follows feeding in apparent y healthy babies has been due to this cause. In some cases I have been delighted at the gre t improvement brought about by an empirical use of Eumydrin.

Before leaving the question of "wind" I should like to say a word about the size of th e holes in teats which are usually supplied to the public. When a baby suckles normally, h e stimulates the unstriated muscles of the milk spaces in the breast, so that if the child is temporarily moved milk is squirted forcibly out. In fact he only has to start sucking move - ments for milk to be literally poured into him. A healthy baby will often get his fill from a healthy mother in a matter of a very few minutes. And yet mothers and nurses have the idea that it is harmful for a child to get his milk too fast from bottles and are alarmed if he chokes. I think he is much more likely to collect wind by having to suck too hard and to take it too slowly. A cold in the nose will upset a baby's feeding because it needs such a little mucus to block his tiny nostrils: and he will feed much more slowly because he has to come up for air and he is bound to swallow some! But with clear nostrils, it is much more likely that air will get into his gullet through sucking at a resistant teat, than that milk will get into his windpipe from too large a hole.

The older child—the child from 4 to 14 who complains of acute abdominal pain which is not the usual "D. and V.", nor due to too many plums or green apples. There is a type of pain which seems to come on for several hours or even days at a time, at intervals of anything from a week to several months: the child appears to be quite distressed, and entirely genuine in his or her complaint: seldom is there vomiting or diarrhœa or a rise in temperature, and the attacks usually subside fairly slowly without giving any clue to the diagnosis.

There are several theories as to the cause. In my young days it was fashionable to call them tabes mesentericus, and the theory was that they were due to acute inflammation of the mesenteric glands. When I was a house surgeon at Paddington Green Children's Hospital, a number of these children were operated upon because the surgeon could not exclude appendicitis. The appendix was completely normal, and occasionally some of the mesenteric glands did in fact appear to be enlarged, but the anæsthetist was a hardened old general practitioner and there was usually a derisive noise from that end of the table.

But if we look at the throat of a child during an attack of abdominal pain, we will often see the early stages of an acute tonsillitis or pharyngitis, which will become established during the next day or two, and make it all too clear that the two are very intimately associated: the tonsils stand sentinel at the entrance to the alimentary canal, so that it is quite possible that an infection which shows itself in its maximal stage at the tonsils and in their glands in due course, can in its stage of invasion extend a good deal farther down the alimentary canal.

The second theory is that it is an allergic manifestation. Where the pain can definitely be related to certain foods, this is certainly an attractive one: eggs, especially duck's eggs, are often more than just indigestible to certain people, and it is interesting to try the empirical use of one of the antihistamines during attacks of abdominal pain in this type.

The third theory is the psychosomatic one. Undoubtedly this is a very strong factor in a great many cases, even if it is not the only one. In our English language we associate emotion with abdominal discomfort: we say "homesick", "lovesick", "sick with apprehension", "sick with joy", "sick with fear", indicating that emotion can cause a spasmodic condition in the bowel. Children are very often secretive about their emotions. They have very little experience of the outside world, and a chance phrase caught from a grown-up can only be translated into an image in their mind from their own experience: the result is that they can have secret apprehensions and fears about the life or health of themselves or their relations which we never dream about, and which in time can certainly cause the type of abdominal crisis which I have described.

And then, of course, there is the time-honoured label of intestinal worms. I believe that it is a very big infestation of threadworms that is needed to cause abdominal symptoms: pruritus ani is caused by them, and sometimes vaginitis, but often the mother will bring a perfectly healthy child along to be wormed simply because she has been scrutinizing his fæces and has found these threadworms. I must admit that I accede to the mother's request, but it is as a treatment for her anxiety rather than the child's ailment.

Constipation.—A conscientious mother will often bring a perfectly healthy child to you saying," Doctor, he hasn't had his bowels open for three days, what shall I do?" Just because she is conscientious, it is very difficult to convince her that this need not necessarily be harmful. With a small baby, a direct stimulus to the rectum is often quite enough to satisfy both mother and infant, and I encourage mothers to use their little finger in a well-soaped rubber finger-stall to stimulate a fæcal evacuation. I think there is a definite place

for a small-sized glycerin suppository, for stimulation from below is to be preferred to an irritating laxative given by the mouth. And yet fæcal retention is by no means uncommon in growing children, especially in school children who often have a very full day, and who will get out of the good habits of the nursery simply because there does not seem to be time to go and have a regular evacuation. It is one of the things which they think can be postponed until absolutely necessary, and it is at school that the habits of constipation are often developed. The advice that I give to these children, and to adults who have gone through this stage of voluntary constipation at school and who have never recaptured the habit of a regular evacuation, is to try to empty the bowel the very first thing in the morning when at any rate the bladder has got to be emptied of necessity. The very presence of the full bladder seems to influence the reflex of defæcation, and the constipated child can so to speak "take his bowel unaware" at this particular time.

One has to be very careful to walk delicately between the two extremes, on the one hand of laissez-faire, and on the other hand of making a child acutely bowel conscious. I think that there is sometimes a place for one of the milder laxatives to be taken regularly each night for a time and just long enough in order to re-establish confidence. And of course the question of proper foods, encouraging the child to take those with a fairly high cellulose residue, along with a reasonable explanation and reassurance, may be all that is needed.

Fæcal incontinence is an interesting condition. Sometimes it is psychological, but it is quite often due to chronic constipation which has resulted in a fæcolith, and I have known several cases where careful bimanual examination with one finger in the rectum and one in the lower abdomen has shown the presence of a soft tumour which moulds itself to the touch, and which has been satisfactorily cleared away with a series of enemas. But the presenting symptom of this condition can be a spurious diarrhœa due to the irritation of the fæcolith, rather than the constipation which one would expect.

The Central Nervous System

The commonest symptom here is headache. I need hardly stress the importance of excluding all the possible causes of headache, for in these days when anterior poliomyelitis is probably the greatest fear of the parent, it is far more common for the general practitioner to see simple cases of headache than in the old days when the parent tended to treat them herself: often all that the anxious mother wants is to be sure that it is not in fact the early stages of that most dreaded of all diseases. Errors of refraction, the eruption of teeth, and mild inflammation of the middle ear will declare themselves if you look for them: but I have been impressed with the frequency of acute headache associated with pharyngitis, often in a child whose tonsils have been removed. I suspect that a sinusitis is much more common than we suppose: for instance, an observant parent brought me a child of just over 2 years saying than an acute headache one day had been followed by a profuse purulent discharge down one nostril, which apparently gave complete relief. At the same time it is difficult to visualize X-raying the sinuses in every child with a headache. I have also observed an acute headache which is associated with a considerable pharyngitis, and which has produced a doubtful picture of encephalitis: lethargy, and unsteadiness in the gait which has not cleared up for a week or two after all fever has subsided and the throat has become clean again. Would the cerebrospinal fluid have shown cells if a lumbar puncture had been done? It is part of the burden that general practitioners carry, that we have to decide how far investigations should be instituted in cases of this type. Nobody likes to have a lumbar puncture done on their own child; there is no very great risk attached to it, but at the same time it is quite a serious diagnostic procedure.

Headache in children has many possible causes. It may be (1) part of the stage of invasion of an acute condition, (2) due to a small undetected local cause (such as those I have mentioned of errors of refraction, eruption of teeth, and mild conditions of the upper respiratory tract), or (3) a symptom which appears and for which we never find a satisfactory cause. It may occur by itself, or it may be associated with an abdominal upset, in which case it is difficult to decide which comes first. So often the cause is psychosomatic. Recurrent "bilious attacks" can be associated with any change from the ordinary humdrum nursery routine, particularly where there is a period of anticipation. It may be getting less common, because in the old-fashioned nursery life was so extremely dull most of the time that the rare treat tended to cause a degree of excitement which our more sophisticated children nowadays would find had to understand.

It is quite common to get cases of migraine with children of school age. Often the main cause is the strain of school life, the approach of examinations combined with the physical competition, and the increasing responsibility in the school. It is an early symptom of stress and it is particularly common in the bright young boy who takes his position in the school seriously, and tries to live up to the promise he has shown. I believe that our educational

system is superior to any other in the world, with a reasonable balance between academi work, physical recreation, and training in responsibility and in self-expression. Freedon for the school child to develop hobbies other than the traditional set games is one of ou greatest achievements since the end of the First World War, but at the same time there i no doubt that school is an extremely exhausting business particularly to the children wh are doing well. In Public Schools, prayers in chapel provide a welcome time of quie relaxation when boys have only to sit looking adequately quiet and attentive, and escap from the continual stress of being chivvied round and expected to do things. They ca even let their minds wander without a sense of guilt and retribution. It is not uncommon to have a boy who really needs twenty-four or forty-eight hours' rest in the sanatorium, no because he is ill, but because the stress of school life has become too much for him: and nine out of ten of these boys first complain merely of headache.

Fits.—In its widest sense, the word "fit" may include anything from a very momentary loss of consciousness to a series of convulsions. If we take a child from birth to the end of adolescence, it is more a rule than an exception that he or she will have suffered at some time from at least one occasion of loss of consciousness. Here again the relationship of the parent to the child is of great importance, for the conscientious parent will often bring a child the very first time such a loss of consciousness has been observed, whereas in other cases the child may have suffered from quite a considerable series of fits before the doctor is consulted. And the question which the family doctor has got to decide is when he shall first allow the word "epilepsy" to be mentioned. For instance, a boy was brought to me at the age of 14 with a story of having had fits in his dormitory on waking up in the morning. He was dazed for a few minutes and that was all. The parents were conscientious and the mother took pains to watch the boy herself in the holidays and saw the same thing. The parents pressed me to send the boy to a consultant, and, with no family history, the consultant was loath to pin the label of epilepsy on the boy, so he had an electroencephalogram done and this showed very doubtful minimum irregularities which could not be said to exclude *petit mal*. The result was that this boy was labelled as a minor epileptic, and on the consultant's advice he was given phenobarbitone for a couple of years. The real crux of the problem arose when he had to sign the declaration for a learner's licence to say that he did not suffer from fits. In view of the two years on phenobarbitone and the possibility of this coming out if he was involved in a motor accident I had to advise him to disclose his history. Although he had been free from fits for a long period without any phenobarbitone, it took two years of very considerable trouble, with visits to several consultants for further electro-encephalograms, before we were able to get the boy finally cleared of the stigma and granted a driving licence. The lesson is plain. In minor border-line cases one should warn the parents that if they raise the question of epilepsy there are certain implications which can be most unfortunate. It means that one must have some yardstick by which to judge and of course here the family history is important. But I like to have two or even three attacks of unconsciousness witnessed by somebody really reliable before I raise the question, then a trial period of control by suitable drugs. If there is a recurrence when the drugs are left off then a positive diagnosis is justified.

And then there is the question of the isolated fainting attack due to anoxia. A rather tired boy of 18 or 20 standing in a crowded smoky room, who feels faint and passes out with a series of clonic convulsions. He often has a short period of mental confusion when he comes round, but I have seen several cases of this nature which have certainly never repeated themselves, and where the wise doctor just waits and sees.

Turning to another problem, how does one distinguish between *chorea* and a *tic?* I find several points helpful. First the history. Although the movements are said to have come on in a moderately short space of time, careful questioning will sometimes elicit an illuminating remark like "of course he has always had a habit of screwing his eyes up, or jerking his hair away, but nothing like so bad as this". A marked tic so often develops from a scarcely noticeable one, whereas with chorea one can say "well, three months ago there was no movement at all". A tic is repetitive, the *same* movement tends to recur, whereas chorea is essentially an intention tremor, so that if one sets a child the task of undressing or writing, chorea will interfere more with the intended movements than a tic will. Observing the child while asleep does not always give one the answer, because the small apparently involuntary movements in sleep are so often the answer to a very small stimulus such as a tickle on the skin or a mild discomfort which causes a change in position. When in doubt it is worth trying a short period of intensive treatment as for chorea, complete bed, sedation and salicylates. A tic is unlikely to improve or may even become more pronounced.

In nearly every condition I have dealt with so far, the mind of the child has been a most important factor. It is here that we can so often help the pædiatrician when we refer a problem to him, for we have the great advantage of continued observation of the child against the background of his home life, and not only does the consultant frequently have

to rely on our description of the actual physical aspect, but we can give him this background, both the heredity and the environment of the child. The parents whom he meets for the first time in his consulting room or hospital are closed books, and yet they are the key to the whole of the child's make-up and outlook on life: and we can provide the consultant with that key by giving a thumb-nail sketch of the home life.

Asthma still remains a most puzzling illness (or rather tendency): with both asthma and enuresis treatment must include equally both parent and child. To my mind one of the most marked features of asthma is the decline in frequency in my part of the world during the last twenty-five years. There used to be quite a regular little group of patients on whom one could rely for several night calls, especially at weekends, and I have always been interested in the pattern of the attacks in the different patients. One young man always had his attacks on Saturday nights, and another one always on Sunday mornings: but I think the most remarkable case was that of a boy at a public school who used to have his attacks with the greatest regularity on Monday mornings when he received a letter from his father. The child's father had been at this school and had been a very successful boy. He had never really grown up so that these early successes remained the great triumphs in his life and he was very disappointed at his son who was not repeating the tradition, as the boy happened to be a singularly negative type. The weekend letters were always full of questions as to how he was getting on and how soon he was going to get into the house XV. The boy's method of protection was an acute attack of asthma, so the housemaster tried the effect of withholding the parent's letter for a day or two and the result completely confirmed our supposition, for the boy's attack was postponed on each occasion until the letter was received.

So often it is over-anxiety and over-protection on the parent's part which contributes in the case of asthma in the child.

Croup is an interesting minor spasmodic condition allied to asthma. I always feel that when a child has an attack of croup it is rather the parting of the ways for the parents of that child: for if they give way to unbridled fear and apprehension then they may easily sow the seeds of asthmatic attacks later on. In the same way I have frequently listened to a child's chest when the child has been hot and breathless and excited and heard a number of rhonchi, I think one should always be extremely careful to avoid the use of the word asthma in any sense until it is necessary to use that label. Miss Fanny Burney says that George III beat "Prinny" when he had attacks of asthma. I will leave it to the psychiatrists to say whether this can be considered as one of the factors which formed his rather distinctive character later on.

Anorexia.—It is so usual for a parent to bring a child because he or she will not eat its food, that I expect most us do say to the parent, "Oh, he's reached that stage, has he?" thereby implying its normality. The more conscientious the parents the worse for the child. Nowadays they often demand an X-ray just to see that there is no mechanical obstruction which is preventing the child from swallowing, or in the case of a ruminator is causing the child to bring back the food, and which it does with such pleasure! Usually the child is young enough for the impression of the X-ray not to be associated with its feeding habits, and so it does little psychological harm: but for an older child I think that it does definitely stress the effect that he is having on his parents, and therefore may harden him in his ways. A child's world is so very small compared with ours, that events which are small to us look very large to them. Time is limitless from their point of view, and the one thing they like is to have a good game with as many players as possible. If they can make a mealtime into a general circus which involves the whole household, so much the better and the greater fun for themselves and hoots to grown-ups who don't appear to enjoy it!

Dr. Wilfrid Sheldon paid tribute to the Address by the Section's retiring President. The opening sentence had pointed out that pædiatrics was general medicine applied to a particular age group, to which the corollary was the necessity for a pædiatrician to have a thorough training in general medicine before branching off into pædiatrics, and thereafter to remain *au fait* with advances in general medicine. The observations which Dr. Barber had made about "wind" and the technical problems of sucklings were so full of common sense that they might well be reprinted and adorn the walls of infant welfare centres.

Although doubts were sometimes expressed about the existence of pylorospasm in infants, there were certainly infants whose clinical story simulated that of pyloric stenosis, and in whom gastric peristalsis might be visible but the typical pyloric tumour could not be palpated. There was usually evidence of feeding errors, especially those associated with either underfeeding or some fault in the technique which gave rise to excessive swallowing of air. While the name pylorospasm aptly described the results it was necessary not to be content with a name, but to determine the underlying causes. The correction of these, combined with a sedative for a few days, would usually bring relief. Dr. Sheldon was rather averse to the empirical use of Eumydrin for these infants, for it could easily lead to the drug being employed in infants suspected of hypertrophic pyloric stenosis before the diagnosis had been firmly established. Most authorities in this country required a palpable pyloric

tumour as the diagnostic criterion, but Eumydrin would maintain the pylorus in such a state of relaxation that palpation of the tumour then became almost impossible, and it was therefore preferable to defer the use of Eumydrin pending an authoritative decision as to the presence or absence of pyloric stenosis.

Within recent years it had become necessary to add hiatus hernia to the list of conditions to be distinguished from pyloric stenosis. The presence of specks of altered blood in the vomited material should be enough to raise suspicion, and lead to the examination of a barium swallow under the X-ray screen, by which hiatus hernia could be identified. In three infants both hiatus hernia and hypertrophic pyloric stenosis had occurred together, but the question of their interdependence remained undecided.

The causal relation between an infection in the throat and abdominal pain was one constantly being brought to the notice of pædiatricians. Another common cause of abdominal pain, or perhaps recurring discomfort would be a better description, met with in the middle years of childhood was chronic indigestion, using this term in a broad sense. The story in these cases usually included a description of the child going deathly white at times, having dark rings under the eyes, and perhaps the tongue being dirty or the breath unpleasant. In some of these children the stools would at times be pale, and yawning or too rapid fatigue might be reported, symptoms which would lead one to suspect that a rich Jersey milk was the cause of the trouble; in other children the story would be of the passage of undigested slimy motions, and then very often the cause would be found to lie in the child's diet having far too much roughage in it.

Dr. Sheldon said that if a child was brought on account of fidgetiness, and in the opening statement the mother named one particular movement, it would almost certainly be found that the child was suffering from a tic, for the movements of chorea were so diverse that no one particular movement stood out as remarkable.

With regard to lack of appetite, especially in young children, the first essential was to record the weight of the child, for sometimes the real situation was that the child would not eat as much as the parents thought it ought to, while in fact they were aiming at too big a target. At all events if the weight was up to or above the average for the age there was obviously no advantage in trying to increase the child's appetite.

Dr. C. B. M. Warren said that one of the pleasant features of the life of a consultant pædiatrician was that much of his work was closely linked with that of the general practitioner. Because children should not go into hospital unnecessarily, pædiatricians had special opportunities for seeing them in their own homes with the family doctor when they were ill with acute but relatively common diseases. Probably in no other specialty did a consultant meet the general practitioner on common ground more often than in this one. How important it was, then, that this pleasant relationship should be preserved.

Dr. Barber had mentioned the child with asthma, an excellent example with which to emphasize the importance of keeping the family doctor in the picture. Sooner or later most children with asthma found their way to hospital. Anxious parents quite reasonably insisted that there should be further investigation. Once the case had been investigated at the hospital, however, and serious disease excluded, the right person to take over the treatment—except in special circumstances—was the general practitioner, who nearly always had an intimate knowledge of the child's social setting and thus was in a better position than the consultant for influencing that to the good. Dr. Warren had never been much in favour of asthma clinics except for purposes of research because he considered that they created the wrong atmosphere for the asthmatic child.

The problem of the child with abdominal pain was common in hospital practice also. For example, a small survey in Colchester had shown that 15% of the children attending the pædiatric outpatient clinic there for the first time had abdominal pain as their main symptom. Sometimes the pain could be related to a minor parenteral infection but more often no cause could be found. Nervous factors, particularly anxiety, must be at the root of the trouble in many cases because it was surprising how often improvement would follow a thorough examination backed up by reassurance of both parents and child.

All convulsions had to be taken seriously and properly investigated; but Dr. Warren agreed with Dr. Barber that a diagnosis of idiopathic epilepsy should not be too readily made, with all that it implied, just because a child had had a single seizure. It might be necessary to take the parents into one's confidence and to tell them what was in one's mind but it was not always necessary to commit oneself to an immediate diagnosis of epilepsy.

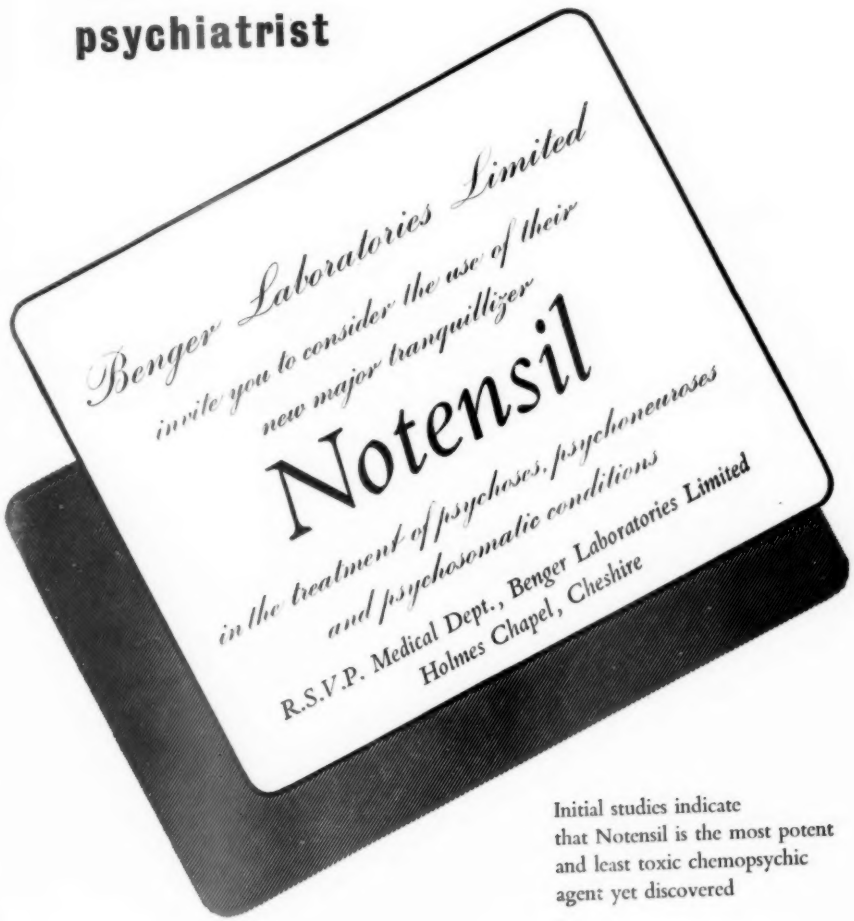
Dr. Warren raised the question of the relationship between those running the Welfare and School Clinics and the general practitioners. A fair proportion of all the children attending his outpatient departments were referred directly from these public authority clinics. Not infrequently they were sent to the consultant clinics for relatively trivial complaints which could reasonably have been dealt with by their family doctors. For example, he had had to see young enuretics whose general practitioners had never even been told about their trouble. It seemed to him that those who worked in isolation from the rest of the profession in Welfare Clinics tended to lose touch with clinical medicine, and that it was because of this that they were not always wise in their handling of a situation. He had seen mothers who had been frightened by what had been said to them about the innocent systolic murmur which had been heard over their child's heart at the clinic. His own feeling was that it would be better to have these clinics staffed by practising doctors, that is general practitioners. The problem was not a simple one, however, because although this might, and indeed did, work well in a small town or country practice, it would be much more difficult to organize such a system for the larger towns. He thought that this whole question of the functions and staffing of the Welfare Clinics could be usefully reviewed.

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Section of Epidemiology and Preventive Medicine

President—IAN TAYLOR, M.D., M.R.C.P., D.P.H.

[*October* 19, 1956]

The Changing Epidemiology of Sonne Dysentery [*Abridged*]

PRESIDENT'S ADDRESS

By IAN TAYLOR, M.D., M.R.C.P., D.P.H.

SONNE dysentery is an epidemiological black sheep. At a time when the intestinal infections as a group have come nicely under control, Sonne dysentery has entered a phase of wild and quite uncontrolled epidemicity. So difficult is it to control that many people would be only too glad to ignore it, if that were possible. Some feel that it is a great mistake to dignify this trifling disease by the name of dysentery, which has such a fearful connotation in the public mind. Many of us at some time or another have turned a blind eye in the hope that we would hear no more about it. Sometimes we have been forced into action for fear of what others may say. The present appears to be a suitable time for taking a look at this disease and studying its recent behaviour.

Although it is probable that the causal organism had been described before, the story of this disease really began with Sonne's description in 1915 of the association of the organism with cases of dysentery in Denmark. The Sonne bacillus was reported in Britain from 1924 onwards, and outbreaks in different parts of Britain from about 1930 onwards. Descriptions of early British outbreaks show many of the features familiar to us to-day. Thus MacGill and Downie in 1932 noted the importance of the school as an epidemic centre, stressing that it was particularly the younger school children who were involved. They thought spread was largely due to close contact, and that mild undetected cases were important in spreading infection. About the same time Pickles (1932) was studying his first outbreak, which took place at the time of the year at which Sonne dysentery epidemics occur nowadays.

However, it was a few years later before things began to warm up. Late in 1937 we read in an editorial in the *British Medical Journal* "During the last few months there has been a notable increase in the incidence of dysentery and diarrhœa, chiefly in children. Small outbreaks have been reported from various parts of England and Wales, but the largest increase has been in London . . ." and later in the same article, "Hitherto in this country Sonne dysentery has for the most part remained localized and sporadic in character, in contrast to its epidemic-endemic prevalence in the U.S.A and Scandinavia". It looks as though in 1937 we were seeing the emergence of Sonne dysentery as a widespread epidemic disease in Britain.

Fig. 1 shows the annual notifications of dysentery in the last twenty-five years. The activity in 1937 and 1938, the beginning of which has just been mentioned, was indeed quite notable by previous standards, although almost insignificant in the light of later events. For those who believe that the common infectious diseases are on the way out this diagram will come as a shock. Not only is dysentery being notified at a very much higher rate than ever before, but there is no indication yet that it has reached peak figures.

How many of the notifications are Sonne dysentery? The Public Health Laboratory Service has published each year a summary of all isolations of *Shigella* by type. In 1945 and 1946, 87% were Sonne. In the next two years incidence was low, and the proportion of Flexner dysentery comparatively high, the percentage of Sonne being 57 and 73. The next year, 1949, the figure was up again to 88%, and since 1950 between 95% and 98% of the isolations have been Sonne. It appears that at least the big changes in notification rate are due to changes in the incidence of the Sonne type.

How much are the higher figures due to improved bacteriological facilities? The growth of the Public Health Laboratory Service, and improving techniques in the isolation of the organism are facts, and it would be strange if they were not reflected in a higher rate of diagnosis of dysentery. The setting up of the service at the beginning of the war may have been responsible for a good deal of the increased incidence between 1940 and 1945. It can have had no relation to the decreased incidence immediately after the end of the war, and it is difficult to believe that any changes in organization and technique that have taken place in recent years can explain the enormous increase in notifications in the 1950s. The increase in the last few years probably represents a real increase in the incidence of Sonne dysentery.

How much of the total incidence of dysentery do the notification figures represent? Some years ago Stocks (1949) estimated that notification of dysentery was only fractional.

This then is the first change in the aspect of Sonne dysentery; an increasing incidence durir g the last twenty years consisting of successive waves, each of which has receded less than it ha s advanced, giving the impression of an incoming tide. Whether the tide has yet reached i s highest level we do not know. The years 1947–1949 appear to be worth further study a s possibly containing the reasons why the wartime epidemic ended and the great prevalenc e of the 1950s occurred. During this study we shall find that a number of important change s in the epidemiology of the disease did in fact occur just at that time.

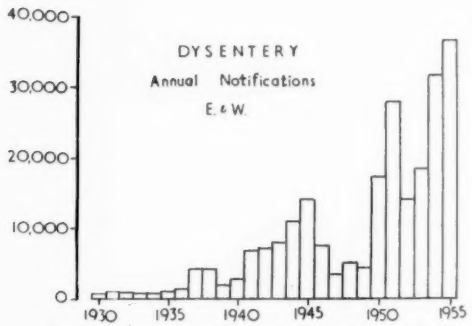


FIG. 1.—Annual notifications in the last 25 years.

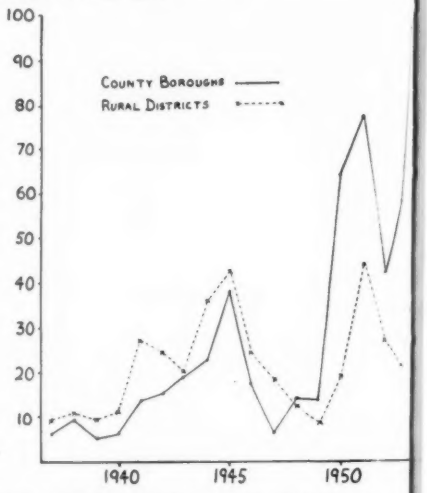


FIG. 2.—Dysentery. England and Wales. 1938–54.→ Notification rates per 100,000 population.

Relation to population density.—During the years in which dysentery has been increasing the experience in the country districts has been quite different from that in the cities. In Fig. 2 the rates for County Boroughs and Rural Districts are shown. It will be seen that up to 1947 the rates in the Rural Districts were higher than those in the County Boroughs, but that thereafter the position was reversed, the disparity between the two types of district being much greater during the last five or six years than before. As far as the Rural Districts are concerned the epidemic of the 1950s has been no greater than the wartime epidemic. It will be noticed that the change-over from rural to urban excess took place during the period of comparatively low incidence after the end of the war. There is no evidence that this change was associated with the wartime evacuation or the return of children to the towns.

The change from rural to urban excess in an infectious disease has been noted before. Greenwood (1935) mentioned it as a change that sometimes happened to a disease when it was in a state of declining incidence, and McFarlan (1951) showed a similar change to be occurring in infective hepatitis in East Anglia in 1946, also during a period of declining incidence. Unlike these examples the change in dysentery occurred during a period of temporary low incidence which was the prelude to the highest incidence ever recorded.

The infectious diseases showing the highest incidence in towns are principally those, such as measles, which spread by personal contact; whereas the most notable example of an infectious disease with a rural excess is enteric fever, a largely food-borne infection. This is a generalization from which there are exceptions. Nevertheless it is suggested that the change from rural to urban excess in Sonne dysentery is consistent with the idea that whereas the disease was at one time spread by a combination of food-borne infection and personal contact, it has now largely abandoned its attempt to be a food infection, and has adopted the far more successful method of personal contact.

Seasonal incidence.—The seasonal incidence of the disease shows equally interesting changes. Fig. 3 gives the maximum notification figure registered in each week of the year from 1947 to 1955. The year's events are shown from nadir to nadir, the diagram running from the 35th week of one year to the 34th week of the next.

In recent years the peak of the dysentery epidemic has been between the 10th and 15th weeks. Following this main peak there is a subsidiary peak about the 20th week. In the curve a peak is also shown about the 50th week, but this is in no way typical and occurred only once during the nine-year period. There is no autumn rise such as is found in enteric fever and food poisoning. This would have been expected between the 36th and the 40th weeks, and such a rise is not seen at all in the dysentery picture from 1947 onwards.

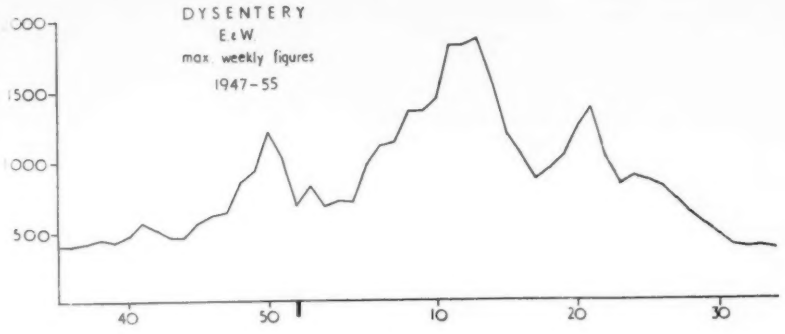


FIG. 3.

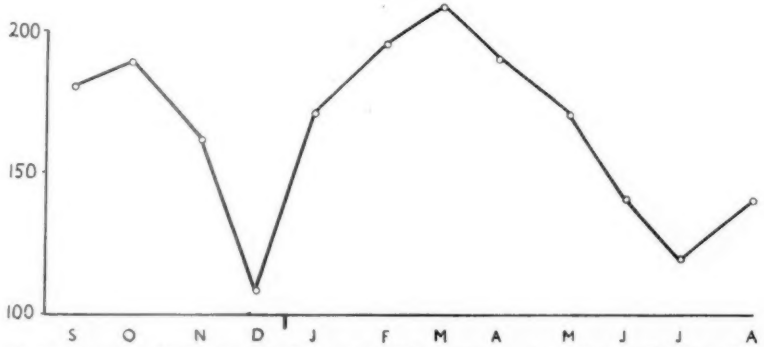


FIG. 4.—Dysentery. England and Wales. Monthly averages of weekly notifications 1941–48. Figures from Glover (1949).

In contrast to this, Fig. 4 is a diagram based on figures published by Glover (1949) for the years 1941 to 1948. Once again the graph begins about the 35th week, but in this diagram monthly averages of weekly notifications are shown. The picture before 1948 was obviously very different from that since that time. The main peak was in March, corresponding to the peak about that time in recent years; but in addition there was, before 1948, a well-marked secondary peak in the autumn, in the months of September and October, at the period of the year in which enteric fever and food poisoning are commonest. The autumn peak, which was present before 1948, has been notably absent in recent years.

This gives further support to the suggestion that the food-borne component has largely disappeared from notified dysentery in recent years. If this is so it is important that it should be generally recognized. Too often do we see the rising figures of dysentery blamed on communal feeding and used unfairly to show how unsatisfactory our food handling methods are.

The idea that dysentery is losing its food-borne component does not rest, however, on indirect evidence only. The figures of reported food outbreaks of dysentery of the Sonne type published by the Ministry of Health and the Public Health Laboratory Service show 41 such outbreaks in the decade 1935 to 1944 compared with only 6 during the period from 1945 to 1954 which was of equal duration but which experienced a very greatly increased incidence of dysentery.

Thus after the year 1947, at which time the incidence of dysentery, particularly Sonne dysentery, was at a low level, the behaviour of the disease has differed in certain respects from that before 1947. It has been more prevalent; it has shown a different relation to population density; it has had a different seasonal incidence; and it has been less associated with food infection than formerly. It is possible that what we have seen is the appearance of a new strain of Sonne dysentery, one that is better adapted to contact infection as a way of life.

Age incidence.—Some years ago Dr. Alison Glover (1947) wrote of dysentery that "the scourge of armies has become the bane of nurseries", pointing out that the disease was largely one of young children. In recent years there have been a number of reports stressing the way in which the disease spreads quickly and widely in families, and it is obvious that an infection of this type cannot remain exclusively in one age group of the population. Davies (1952) reported the examination of 234 home contacts of cases. Half of them became infected, the proportion varying from 37% of the adults, to 50% of the children aged 8 to 15, and about 80% of those under 7 years of age. These findings have been confirmed by other workers, notably Shaw (1953) and Ross (1955).

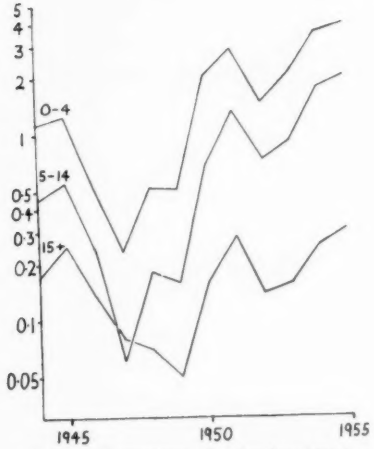


FIG. 5.—Dysentery. England and Wales. Age specific notification rates per 1,000 population.

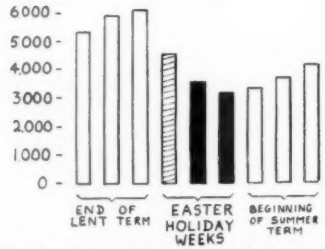


FIG. 6.—Dysentery. England and Wales. Total weekly notifications 1951–55.

It is not surprising, therefore, that a diagram (Fig. 5) of the age specific notification rates over a number of years shows that incidence from year to year has gone roughly parallel in the various age groups. The main exception was in 1947, when for one year the adult rate was higher than that in children of school age. In that year there was a very low incidence of dysentery, coupled with one or two sizable outbreaks of Flexner dysentery in mental hospitals. It is probable that had it not been for the Flexner outbreaks the curve of incidence in the over 15 age group would have shown a dip downwards like those at other ages.

A rise in the percentage of notifications coming in the 5 to 14 years age group in recent years is mainly due to the post-war rise in the birth-rate, but there has also been some degree of closing up between the attack rates in the 0 to 4 years and the 5 to 14 years age groups.

The main focus of activity in Sonne dysentery has now become the primary departments of the schools, where outbreaks are becoming quite frequent.

In view of this association with the schools one would expect to see some evidence of a connexion between the school calendar and the incidence of dysentery. The most constant features of the seasonal curve are the summit of the main peak and the bottom of the trough between that and the following subsidiary peak (Fig. 3). To study the possible relation between these features and the Easter holidays the weekly notifications of dysentery in England and Wales over the five-year period from 1951 to 1955 were taken and arranged not by date, but in relation to the Easter holidays. The dates of the London school holidays were used for this. It is the practice to break up in the middle of a week and to have two and a half weeks' holiday from this time. In Fig. 6 the two black columns are weeks of complete school holiday in London, and the shaded column is half school and half holiday. The height of each column represents the number of weekly notifications in England and Wales.

It is seen that the incidence of dysentery increased steadily during the last three full weeks of the school term; that the beginning of the holiday saw a marked fall in incidence which was maintained through the holiday; and that as soon as the schools reassembled incidence began to rise again towards the secondary peak in the summer term. A somewhat similar picture is seen when figures for individual years are studied. It appears that the main

epidemic is cut short by the break-up of the schools, and that it recovers its momentum when the new term begins. It is not suggested that the schools provide the main impetus for the dysentery epidemic; but there is some evidence that the opening and closing of the schools are responsible for some of the irregularities of the epidemic curve.

Geographical incidence.—When recent incidence in the Registrar-General's Regions is studied we find, in general, a lower incidence in the South and West of the country than elsewhere. This may be due to the tendency already mentioned for incidence to be higher in urban areas than elsewhere.

When comparing one town with another great differences may be due to such causes as variations in the activity of the health department in the search for Sonne, the existence of a public health laboratory in the town, the presence or absence of day nurseries, and many other factors. In most of the large towns there has been a general tendency towards higher incidence in recent years. Nevertheless a high rate in one year has not always meant a high rate for all time. Some of the large cities have managed to get comparatively clear after very high incidence. With regard to the low incidence in the South and West Regions mentioned above it is of interest to note that whereas Plymouth and Portsmouth have both had low rates Cardiff and Bristol have both experienced comparatively high rates. Stoke, Birmingham, and Coventry form a persistent low incidence group in the Midlands which has weathered the storm that has raged about it. It is difficult to find any general rule governing incidence in the large towns in recent years.

The distribution of dysentery in London in recent years has been interesting. Three two-year periods of high incidence were chosen, viz. 1944–45, 1950–51, and 1953–54, and a list was made of the Metropolitan Boroughs in London which had an incidence of more than 1 case per 1,000 population in all three of these periods. Nine Boroughs were in the list. With the exception of Chelsea all the high incidence Boroughs formed a compact block ranging from St. Pancras, Islington, and Stoke Newington in the north, through Finsbury, Shoreditch, Bethnal Green and Stepney further south, to Bermondsey on the south side of the river. The high figures in Chelsea had been inflated by repeated high incidence in a single establishment and a comparatively small population. The compact area in north London was surprising as the distribution of disease and of the various social and environmental factors in London tends to be extremely patchy. The distribution of high dysentery incidence did, however, appear to have some relation to at least one of the environmental indices, namely the average number of persons per room as shown at the Census. With the exception of Chelsea all the high dysentery Boroughs had overcrowding figures (based on persons per room) above the average for the County.

In an inquiry carried out by the Joint Committee of Medical Officers of the London County Council and the Metropolitan Boroughs in 1953 it was found that 16% of the persons notified as dysentery in a year were living in conditions of more than 2 persons per room, the figure for the whole population at the Census being 5·3%. In the same inquiry a higher secondary attack rate in families was found when crowding was present than elsewhere.

Prevention and Control

There are some who think that the prevention of dysentery lies in the washing of hands. Others feel that the disease is uncontrollable. Between these extremes the majority attempt to control the disease with varying degrees of hope and despair, success and failure.

Most will agree that when the disease is present we should do what we can to prevent its spread. Nevertheless this does not mean that we should go on automatically repeating standard procedures regardless of whether they are successful or not. We should consider all our preventive measures in the light of the circumstances of each outbreak, and use only those that have a reasonable expectation of success.

For the present, prevention must, perforce, be limited to the mitigation of local epidemics. There are three main lines of attack on any infectious disease, namely eradication of the reservoir of infection, prevention of transmission of infection, and specific immunization. The prospect of immunization against Sonne dysentery does not look hopeful at present.

The reservoir of infection consists of infected human beings. A great deal of bacteriological examination of contacts is carried out in institutional, nursery, school, and family outbreaks. In bringing to light infected persons who may be in need of treatment this work is obviously valuable; in the prevention of further spread results are uneven, and the reasons for success or failure are not fully understood. The earlier in the outbreak that one begins the better the expectation of success. However, the bacteriological approach is limited by the technical factors involved. Even at the most favourable estimate one cannot expect a bacteriological result until the day after the specimen is taken, and by this time the epidemiological picture may have changed, because Sonne dysentery spreads with such speed. The routine and repeated bacteriological examination of contacts is one of the measures which should be examined with a view to relating the labour involved to the results achieved.

A possible partial solution which deserves further thought is that suggested by Dr. Harry Hawke in a letter to Dr. Bill Brewer, the 25th letter in the Widdicombe file, describing a school epidemic of the Merrygowhimbles (*Lancet*, 1955). He suggested advising the head teacher merely to watch and pray and to see that nobody with diarrhœa cooked or served food; four weeks later he would wish to examine the fæces of the whole school and "smite those *Shigellæ* which linger". This could not be the pattern for all incidents, but on occasions where the initial bacteriological survey discloses that infection has spread wider than expected, farther bacteriological surveys might well be postponed until a time when they can be undertaken more purposefully.

A good deal of the impetus for bacteriological examination of contacts comes from the belief that symptomless excreters are of more importance than cases in the spread of dysentery. There is in fact a certain amount of evidence that the reverse is the case. In the inquiry carried out in London in 1953 to which reference has already been made, it was found that the secondary attack rate in families was considerably smaller when the primary case was a symptomless excreter then when the first case had diarrhœa. Ross (1955) has produced confirmatory evidence on this point.

Once the case or carrier is brought to light the question of putting him out of circulation arises. This often raises the subject of admission to hospital. Easton (1955) has written a strong condemnation of the policy of sending Sonne dysentery patients to isolation hospital, and the more one examines this subject the less justification there appears for using the hospital in this way. Only a very small proportion of cases really require hospital treatment; and removal to hospital can have little effect on the spread of infection. Moreover there are disadvantages in hospital admission, such as expense to the community, the danger of cross infection, and the psychological upset to the child. Unless the home circumstances are totally unsuitable there can be little justification for removal to hospital except in the rare case that must be admitted for treatment that cannot be given at home.

The other form of attack on the reservoir of infection is the direct attack on the organism. It is true that the trials of sulphonamide prophylaxis in day nurseries were not encouraging, but there may be many reasons for this, and this line of attack is surely worth pursuing farther. What is required is a drug that is cheap and effective in quickly and permanently rendering an infected person negative, and which can be given in general practice to sufferers and their family contacts. The disease with which we are dealing is so mild that the drug used must be quite free from side-effects.

The last method of prevention is control of the transmission of infection. The extreme rapidity with which the disease spreads in a closed or semi-closed community makes one wonder whether infection may sometimes be carried by the indirect air-borne route. The organism has occasionally been recovered from dust in the environment of cases. It is not suggested that this is an important method of spread, but we should, perhaps, keep an open mind on the possibility that it may sometimes operate.

If there were ever any doubts about the principal mode of spread of the disease they have surely been abolished by the painstaking demonstration by Hutchinson (1956) of the manner in which children constantly infect their hands from lavatory seats, and the methods by which the seats become infected. This clear demonstration deserves a thorough follow up; a known risk of this kind cannot just be accepted quietly. However, the difficulties should not be underestimated. It is not only a matter of making people wash their hands. The whole subject of the design, method of use, and management of the lavatory is involved. It is a humiliating fact that after 100 years of main drainage the organization of the prevention of lavatory infection, particularly among groups of children, remains one of our biggest problems.

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Section of Medicine

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Malignant Carcinoid Tumours

By REGINALD E. B. HUDSON, M.D.

Institute of Cardiology and National Heart Hospital, London

AMONG the lining cells of the mucosa of the intestine and elsewhere there is a very small proportion of yellow cells which have an affinity for silver stain. These cells were first demonstrated by Kulschitzky and are therefore known as Kulschitzky's yellow cells. Later, Masson showed their affinity for silver stain and so they are now called argentaffin cells. They are thought to be the origin of argentaffin tumours. Since 1907, these tumours have been called "carcinoids", but they are better described as argentaffin carcinomas. Though the majority are relatively benign and quite common, a few can become very malignant and it is this type of metastasizing argentaffin carcinoma which, in the past three to four years, has been recognized as being associated occasionally with cardiac lesions in a well-defined syndrome.

The primary tumour and its metastases elaborate an excess of the hormone serotonin (5-hydroxytryptamine), which is carried in the portal and hepatic veins to the heart. When it reaches the lungs, however, the serotonin excess is removed by the lung enzyme, monoamine-oxydase, which converts the serotonin to 5-hydroxy-indole-acetic-acid. This is excreted in the urine and the detection of an excess is therefore used as a screening test for the presence of argentaffin carcinoma.

Only those parts of the heart which have been bathed with large amounts of serotonin show major lesions so it follows that, normally, the chief changes are confined to the right heart, particularly the tricuspid and pulmonary valves.

The characteristic syndrome is that of tricuspid or pulmonary stenosis (or both) in a patient who has the symptoms of flushing attacks, especially after meals, bronchial asthma and diarrhœa.

CASE REPORT

Woman of 33 was admitted to the National Heart Hospital under Dr. Paul Wood for investigation of pulmonary stenosis. It was soon realized that this might be associated with argentaffin carcinoma because she had the typical symptoms, and nodules could be palpated on the liver surface. Catheter studies were made and the findings published by Goble, Hay and Sandler (1955). Sir Russell Brock removed the primary tumour from the ileum and some liver metastases. She then had various treatments including radioactive gold, which relieved the symptoms a little but caused severe neutropenia from which she recovered. The subsequent course, however, was one of pathetic mental and physical deterioration leading to her death two and a half years after the onset of symptoms.

Pathology.—The primary tumour, removed at the Brompton Hospital, was situated in the ileum raising the mucosa into a lump about the size of the thumbnail. Histology proved it to be an argentaffin carcinoma, as did the liver biopsies.

At necropsy, there was much emaciation. The skin incision and end-to-end anastomosis in the ileum were both perfectly healed. The findings are presented in the order of the circulation.

The *liver* was enlarged to 2,200 grams and studded with rounded metastases, some of which were visible on the surface. Several nodules formed a confluent mass in the right lobe. Histologically the appearances were those of argentaffin carcinoma—the cells being arranged in neat masses in direct contact with blood in large sinusoids. The *heart* was not enlarged, weighing 250 grams. The right atrium was normal to the naked eye, but microscopically showed patchy thickening of the endocardium. The tricuspid valve was moderately stenosed and strongly resembled that in chronic rheumatism. The cusps were much thickened and fibrous, adherent at the commissures, and the chordæ tendineæ greatly thickened and shortened (Fig. 1). On section, the cusp thickening was seen



FIG. 1.—Tricuspid valve displayed to show the thick fibrotic cusps and the thick shortened chordæ tendineæ. Note the small warty projection on the endocardium at the junction of papillary muscles about the middle of the left-hand cusp.

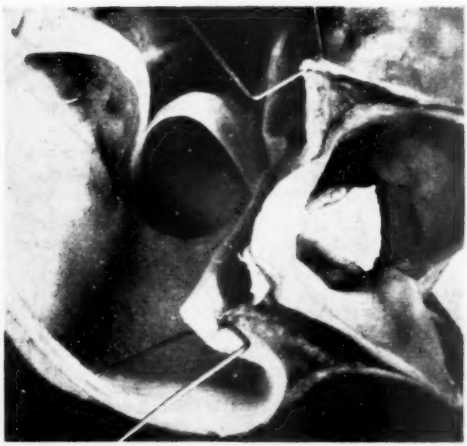


FIG. 2.—Unopened pulmonary valve from above on the right showing triangular stenosed orifice, the thickened shrunken cusps and small sinuses of Valsalva. Aortic valve on left normal apart from some thickening in sinus of Valsalva of upper cusp.

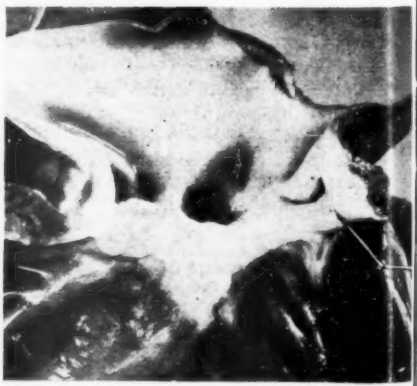


FIG. 3.—Pulmonary valve cut open to show the massive fibrosis involving the cusps and making a "waist" between the pulmonary trunk and the infundibulum. Note the fibrosis extends down into the infundibulum.

to be due to masses of fairly acellular fibrous tissue, without cell reaction or evidence of recent thrombus formation. The right ventricle showed early hypertrophy. The pulmonary valve was even more affected than the tricuspid; the orifice was stenosed to a triangular shape and the cusps greatly shrunken, thickened and hard with fibrosis (Fig. 2). The sinuses of Valsalva were greatly reduced as a consequence of this process, which caused a "waist" between the infundibulum and the pulmonary trunk. There was some spreading of the fibrosis down into the endocardium of the subvalvular infundibulum (Fig. 3). Histologically the appearances were like those of the tricuspid valve—masses of fibrous tissue without cell reaction.

The *lungs* proved to be showered with tiny metastases, the largest being only 1–2 mm. across; one section revealed cancer cells in a lung capillary. In addition, there was early bronchopneumonia.

The *left heart* appearances were practically normal, contrasting strikingly with those of the right heart. There was a little endocardial thickening in the left atrium which was otherwise normal. The mitral valve was normal macroscopically, but microscopy revealed a recent thrombotic lesion on a cusp (Fig. 4). The aortic valve, too, was virtually normal though there was some thickening

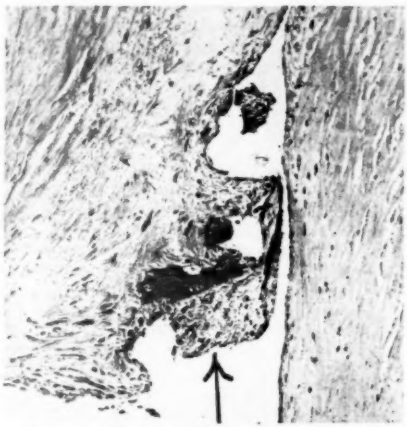


FIG. 4.—Mitral valve cusp. The arrow points to a projecting lesion, probably thrombotic. (Hæmatoxylin and eosin. Low power.)

at the base of one of the cusps. It is feasible that these trivial left heart lesions were associated with the lung metastases, or possibly with an excess of serotonin getting through the lung barrier.

No lesions were found in the brain, kidneys, or in other organs.

DISCUSSION

It seems extraordinary that the description of this new syndrome has lagged half a century behind the first accounts of argentaffin tumours. The condition is undoubtedly rare, and it is possible that in the past any heart lesions found might have been thought to be congenital and not associated with argentaffin carcinoma. Although it has not been shown that serotonin itself is the cause of the cardiac lesions, this is the first disease in which a hormone has been demonstrated to be closely associated with valvular lesions of the heart.

If we are to discover an agent, if such exists, which is associated with predominantly left-sided heart lesions—as in rheumatic fever—it will be found in arterial blood coming from the lungs, and it will exert its major effects on the left atrium and the mitral and aortic valves. Thereafter, it might be removed by the liver and only when it is in such excess as to pass this barrier will it produce sclerotic lesions in the right heart. Such a sequence of events would explain why, in rheumatism, tricuspid and pulmonary valve lesions do not occur in the absence of lesions of the mitral and aortic valves. To my mind, this is the most important aspect of the discoveries associated with the study of argentaffin carcinoma—namely, that such discoveries might lead to advances in our knowledge of the disease process in a far more common disease, rheumatic fever.

Figs. 1, 2, 3 are taken from Goble *et al.* (1956) *British Heart Journal*, by kind permission.

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Malignant Carcinoid Tumours

By R. S. Stacey, M.A., M.D.

University Reader in Therapeutics, St. Thomas's Hospital Medical School, London

Twenty-six years ago Sir Maurice Cassidy (1931) showed to the Clinical Section of this Society a patient who suffered from severe flushes, recurrent attacks of watery diarrhœa, pain in the chest and dyspnœa. The flushing was much exaggerated during emotion and during a meal and there were numerous dilated venules of recent origin over the nose and cheeks. The skin of the trunk was mauve coloured but was liable to sudden changes to vermilion. There was a harsh systolic murmur down the left sternal edge and the liver was large, hard and irregular. This was the first published case of a syndrome afterwards described by Biörck *et al.* (1952) who were the first to associate it with a metastasizing carcinoid tumour of the intestine.

Clinical findings.—Attacks of *watery diarrhœa* have been present at some time in nearly all the cases described. Many of these patients have extensive abdominal carcinomatosis and others have had a resection of gut, but this symptom has also been found in cases where the primary in the intestinal wall was quite small and it has persisted after a small local removal. So it seems likely that the diarrhœa may not always be due entirely to mechanical factors.

The Flush

The description I have quoted from Cassidy's account is typical of cases with well-developed symptoms. In others the skin may be normal most of the time; then a flush starts, usually affecting the face first and then sometimes spreading to the neck, chest and limbs. It may be indistinguishable from a menopausal flush. The colour is usually rather a dusky red but may be cyanotic; or bright red areas may be mingled with areas of cyanosis or even of pallor. In Cassidy's case, flushes were precipitated by a heavy meal and this has been noticed in subsequent cases though not all. Two patients shown me by Dr. P. J. D. Snow in Manchester had noticed that half a pint of beer would cause an attack and in one of them as little as 10 ml. 10% alcohol could be relied on to bring it on. In another case, in which emotion precipitated flushing, a few micrograms of noradrenaline injected intravenously was effective. As time goes on the flushes may become more and more severe, last longer and finally the skin may take on a permanent dusky colour, become coarse in appearance and show the dilated venules described by Cassidy.

During a flush the blood pressure usually remains normal, but may fall and the pulse-rate is often increased; sometimes there is abdominal colic or evacuation of the bowels or bladder and sometimes there is an attack of dyspnœa in which there may be signs of bronchospasm. That is to say the flushes may be accompanied by evidence of plain muscle contraction in various parts of the body.

Dyspnœa due to cardiac failure and associated with ascites and œdema is seen in cases with damage to the right side of the heart. This is one of the most remarkable features of the condition and has already been described by Dr. Hudson. Finally in nearly all the cases in which general symptoms have been present, the liver has been large and hard due to metastases.

Widespread, apparently unrelated symptoms such as these might suggest a humoral agent and a lead was given to the search for this by the suggestion made by Erspamer (for references *see* Erspamer, 1954), while working in an entirely different field, that the argentaffin cells of the intestine, from which carcinoid tumours originate, may secrete 5-hydroxytryptamine (5-HT). In 1953 Lembeck estimated the amount of this substance in a carcinoid tumour and found a very high concentration. In 4 patients (Table I) from whom I have had material

Table I.—5-HT in Carcinoid Tumours
(amount found per gram wet tissue)

Case	Primary	Secondary
II	—	0·6 mg.
III	0·3 μg.	0·08 μg.
IV	0·8 mg.	0·7 mg.
V	—	1·1 mg.

the amount of 5-HT in the tumour tissue fell between 0·6 and 1·1 mg. 5-HT/gram wet tissue in 3 of them. In one, which on other grounds was certainly a case of malignant carcinoid, less than 1 μg. 5-HT/gram wet tissue was found in both primary and secondary; this is no more than is found in normal intestine.

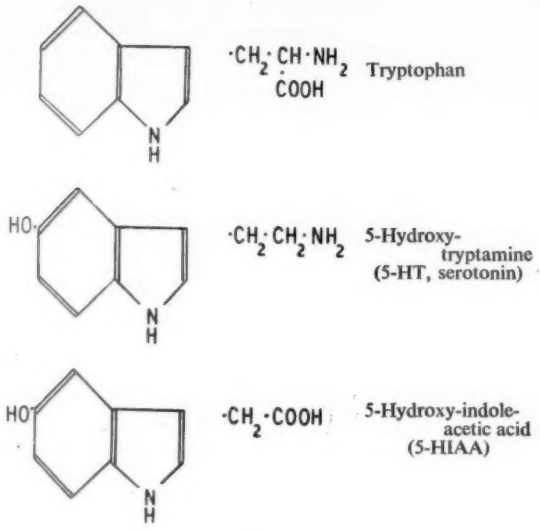


FIG. 1.

5-HT is formed in the body from the essential amino acid tryptophan (Fig. 1) and is subsequently partly oxidized to 5-hydroxy-indole-acetic-acid (5-HIAA), which is excreted in the urine. Normally the urine contains about 6 mg. 5-HIAA per day but in cases of malignant carcinoid this is increased at the very least five or ten times (that is to 30 to 60 mg. per day) and may rise as high as a gram or more per day. Animal experiments show that only about one-third of injected 5-HT can be accounted for as 5-HIAA. What happens to the rest is not known but it is probably safe to assume that 5-HT production is about two to three times that indicated by the 5-HIAA excretion. The detection and estimation of the large amounts of 5-HIAA found in patients with malignant carcinoid tumours is simple and this provides the easiest laboratory method of confirming the diagnosis. There is at present no other condition known in which a large increase in the excretion of 5-HIAA takes place and the finding of this therefore constitutes proof of the presence of a malignant carcinoid tumour.

5-HIAA combines with Ehrlich's aldehyde reagent to give a blue colour and this has been used as a test, but the test described by Sjoerdsma *et al.* (1955) is more satisfactory and can be done in a few minutes. It depends on coupling 5-HIAA with α-nitroso-β-naphthol to give a purple-coloured substance. When applied as described by the authors the test is negative when normal amounts of 5-HIAA are present.

More precise information as to the amount of 5-HIAA excreted may be obtained by the quantitative method of Udenfriend *et al.* (1955) or the shorter method of Macfarlane *et al.* (1956) both of which depend on the reaction mentioned above, or by paper chromatography (Curzon, 1955; Hanson and Serin, 1955; Jepson, 1955).

Amounts of 5-HT found in the blood and urine. Normally 5-HT in the blood is contained entirely in the platelets. Platelets have a great affinity for it and will absorb up to five times as much as they normally contain (Hardisty and Stacey, 1955). This is, no doubt, one reason why there is virtually no free 5-HT in plasma. But a more important reason is that any free 5-HT is oxidized by enzymes in lung, liver, kidney and other organs. When blood clots the 5-HT in the platelets rapidly escapes and part passes into the serum, where it can be estimated, and part into the red cells, where it is lost. There is therefore considerably less 5-HT in serum than in the blood from which it is derived but serum estimations nevertheless provide a rough guide to the amount of 5-HT in the blood provided the method of preparing the serum is standardized. The blood 5-HT and the urine 5-HIAA excretion of 5 cases of malignant carcinoid are shown in Table II. In all both were increased but whereas the average blood 5-HT was only increased eight times the normal, an expression no doubt of the limited capacity of platelets to carry 5-HT, the average 5-HIAA excretion was nearly eighty times that of the normal.

TABLE II.—BLOOD 5-HT AND URINE 5-HIAA IN 40 NORMAL SUBJECTS AND IN 5 PATIENTS WITH MALIGNANT CARCINOID TUMOURS

	Blood 5-HT. μg./ml.	Urine 5-HIAA mg./gram creatinine
Normal: mean ± S.D. (Snow *et al.*, 1955)	0·16 ± 0·06	3·6 ± 1·3
Carcinoid: mean	1·15	280
range	0·4–2·2	22–1,230
Carcinoid/Normal	8	78

Both on account of ease of estimation and the greater abnormalities found, urinary 5-HIAA estimation is the estimation to be preferred to establish a diagnosis.

The urine normally contains only traces of 5-HT and Table III shows the amounts found

TABLE III.—5-HT AND 5-HIAA IN URINE

Case	μg. 5-HT/ml.	μg. 5-HIAA/ml.
I	0·65	70–400
II	0·4	100–2,000
III	20	7–44
VI	0·6	100
Normal	0·01–0·7	1–5

(Lembeck and Neuhold, 1955)

in 4 cases. In 3 of these the excretion was within normal limits, though all were excreting very large amounts of 5-HIAA; in one it was high and this has been verified on numerous occasions.

We have, then, clear evidence that large amounts of 5-HT are formed by carcinoid tumours and that this reaches the blood stream, is oxidized to 5-HIAA and other substances and is excreted. 5-HT is pharmacologically a most active substance; 5-HIAA is inert. We now come to the question: How far are the symptoms of patients with carcinoid tumours explicable in terms of the known actions of 5-HT?

5-HT contracts plain muscle and infusions in man cause diarrhœa, intestinal colic, evacuation of the bladder and bronchospasm. These are all effects met with from time to time in this condition. Infusions also cause flushing and large doses may cause a patchy cyanosis; here again there is a correspondence between the actions of 5-HT and the symptoms to be explained but exactly how these changes are brought about is not clear. 5-HT is a vasoconstrictor and increases peripheral resistance, but whether the flush is due to the effects of stagnant anoxia on the skin vessels, or to venous constriction or some other mechanism, has not been investigated.

The effects of 5-HT on blood pressure are complex. In man and in experimental animals, a rise, a fall or, more often, a fall followed by a rise may be obtained under different circumstances. Apart from the peripheral constriction I have mentioned, it constricts pulmonary vessels and also tends to cause a reflex fall in blood pressure by stimulation of afferents arising in the heart, pulmonary circulation and carotid bodies. Usually patients with malignant carcinoid have a normal blood pressure but until more is known of the circulatory effects in man it is idle to go into this question in greater detail.

By an action on the chemo-receptors of the carotid body, 5-HT stimulates respiration; and this action may play a part in the attacks of dyspnœa.

The pathogenesis of the cardiac lesions remains at present unexplained. The pouring of 5-HT into the portal and hepatic veins probably leads to high concentrations free in the plasma where normally there is little; and this would be largely removed in the lungs. So that if the changes in the heart are due to the action of 5-HT it would be the right side of the heart which might be expected to be the more affected—as indeed it is. Finally 5-HT has been shown to have an antidiuretic action and, on injection into the 3rd ventricle, striking cerebral effects. No changes in patients have been found which could definitely be attributed to these actions.

Cassidy's description, given here twenty-six years ago, shows that he considered the possibility of one humoral agent, namely histamine being responsible for the flushing, for he describes observations in his patient on the triple response and on the injection of histamine. Recently Waldenström and Pernow announced the finding of large amounts of histamine in the urine and plasma of 3 patients with this condition and offer two interesting suggestions

in explanation. Very high concentrations of 5-HT are known to release the bound histamine of the tissues but whether the concentrations reached in man are sufficient to do this is by no means certain. Their second suggestion is that possibly the same decarboxylase which converts 5-hydroxytryptophan into 5-HT may also convert the amino acid histidine into histamine and that the presumed high concentration of this enzyme in carcinoid tissue may lead to a large production of histamine. This is a matter which can be settled experimentally. In any case it seems that not all patients with malignant carcinoid excrete abnormal amounts of histamine, for of 2 cases I have personally investigated one did and the other did not. The reason for this difference and what effect the presence of large amounts of histamine may have on the symptomatology remains to be determined.

Treatment.—There is, of course, very little that can be done as there are invariably liver secondaries present. Surgical removal of malignant glands has been reported to have been followed by some amelioration of symptoms but surgery carries a definite risk. A severe attack may be precipitated by handling or pressing on malignant tissue and I know of 2 cases in which an attack, ultimately leading to the death of the patient, developed at an early stage in the operation before there was any manipulation of the growth. Temporary improvement has been twice reported after ^{198}Au and deterioration twice after radiotherapy.

Potent antagonists to 5-HT are known but so far they have not shown themselves to be of much value in treating these cases. Bromlysergic acid diethylamide, chlorpromazine and dibenyline would appear to be the most promising for a trial. In view of the precipitation of attacks by excitement and by noradrenaline, the use of adrenaline in treating bronchospasm would seem inadvisable. Finally in cases where large amounts of histamine are excreted it is possible that some amelioration of symptoms might be obtained from antihistamine drugs.

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Endomyocardial Fibrosis

By J. Donald Ball, M.R.C.P.

Miners' Chest Diseases Treatment Centre, Llandough Hospital, Penarth

Fibrotic thickening of the endocardium of the ventricles may be seen in myocardial infarction, as a congenital lesion in childhood and sometimes in rheumatic heart disease. In Africa it commonly occurs without any of these associations. In Uganda at least this condition, which has been called by Davies "endomyocardial fibrosis" (1949), is so common that it is one of the three main causes of heart disease, being responsible for 15–20% of all heart failure. (Nephritic hypertension and syphilitic aortitis are the other two.) (Williams *et al.*, 1954.)

This condition has been reported from several regions in Africa. In Sudan (O'Brien, 1954), Northern Rhodesia (Buck, 1954) and Southern Rhodesia (Gelfand, 1954) it is fairly common. A number of cases have been seen in Nigeria (Nwokolo, 1955; Beet, 1954). From this region come the only three examples of the disease in Europeans (Gray, 1951; Edge, 1946). Other reports come from the Gold Coast (Hughes, 1953; Edington, 1954) and Gambia (McFadzean, 1953). In contrast very few examples of the disease have been recorded outside Africa. Only 4 cases in the American literature on obscure heart disease can be accepted as identical (Fienberg and Holzman, 1951; McKusick and Cochran, 1952;



FIG. 1.—*Left ventricle.* Lower half of the ventricular endocardium is greatly thickened. Fibrosis of the inner half of the myocardium at the apex. Ante-mortem thrombus has been cut across at the apex. Mitral valve is not yet affected. (Male aged 65; the main lesion was in right ventricle with massive thrombosis.)



FIG. 2.—*Left ventricle and mitral valve.* Small foc of endocardial fibrosis seen at apex. Posterior cusp mitral valve thickened and completely adherent fibrotic endocardium on upper part of posterior w (Male aged 50; died of pneumonia.)

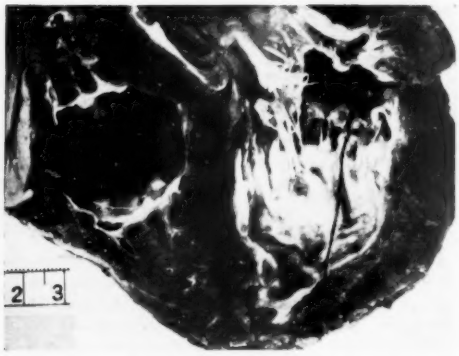


FIG. 3.—*Left and right ventricles.* Left ventricular endocardium almost entirely covered by greatly thickened endocardium. Thin layer of dark thrombus at apex. The right ventricle shows advanced obliteration of the inflow tract. A small crypt lined with thick endocardium marks the site of the old apex. (Male aged 56: died from left and right heart failure of one year's duration.)



FIG. 4.—*Tricuspid valve and right ventricle.* Gross distortion of the valve with marked stenosis. The posterior cusp has completely disappeared beneath a mass of thickened endocardium. The anterior cusp is a short rigid band of fibrous tissue. The ventricle shows advanced obliteration of the inflow tract. (Male aged 30; died after two years in right heart failure.)

Hoffman *et al.*, 1955; Clark *et al.*, 1956). Two of these cases had spent war years in the Pacific islands. A similar number of cases from the European continent are recorded, mostly from Switzerland (Löffler, 1936; Fossel, 1942; Egger, 1944; Brinkman and Prior, 1950). No patient so far has contracted the disease in Great Britain.

Pathology

The heart shows four main lesions (Davies and Ball, 1955):

(1) In the left ventricle, the endocardium of the apex may be greatly thickened and fibrotic (Figs. 1, 2 and 3). It presents a smooth white surface, and may be 1–5 mm. thick. The margins of the fibrotic area are commonly sharply defined. The lesion may spread on to the posterior, lateral and anterior walls but usually spares the septum. The fibrous tissue penetrates the inner third of the myocardium. Ante-mortem thrombus is common on the surface, and calcification in the depths of the lesion.

(2) The mitral valve: The posterior cusp and its chordæ become thickened and eventually bound down to the posterior wall of the ventricle, rendering the valve incompetent (Fig. 2). Mitral stenosis is occasionally seen without any evidence of rheumatic heart disease.

(3) The right ventricular endocardium shows lesions which resemble the left with one exception, the obliteration of the inflow tract of the ventricle. This distortion of the anatomy brings the apex towards the tricuspid valve until the length of the inflow tract is halved (Fig. 3).

(4) The tricuspid valve is involved in a manner similar to the mitral though severe involvement is less frequent. Stenosis is present occasionally (Fig. 4).

Clinical Findings

Patients of both sexes and all ages are liable to the condition (Ball *et al.*, 1954). Our youngest patient was a boy of 4 years. The symptoms and signs depend on the region of the heart predominantly involved. In left-heart lesions the outstanding complaints are the dyspnœa, ascites and œdema of heart failure. If the mitral valve is incompetent a loud, high-pitched systolic murmur and thrill are present at the apex. The heart shows general enlargement radiologically; left atrial enlargement, sometimes with systolic expansion, is present with mitral incompetence.

If right-heart lesions predominate, œdema and ascites are prominent but dyspnœa usually absent. Jugular veins are distended but the signs of tricuspid incompetence—jugular and hepatic systolic pulsation and tricuspid systolic murmur—are usually absent even though necropsy shows gross distortion of the valve to have been present. The explanation for this absence of the signs may be found in the extensive deposits of fibrous tissue on the walls of the right ventricle, which is perhaps thereby prevented from exerting its full systolic thrust. These patients may be very difficult to distinguish from those with constrictive pericarditis; thoracotomy has sometimes had to be performed in the hope of finding a removable lesion.

Ætiology

The cause of the condition remains unknown but certain possibilities demand special consideration:

(1) *Malnutrition.*—Although this was originally suspected in Uganda, recent observations have not confirmed it. Patients are no more malnourished than their fellows. Injections of thiamine produce no response. Vitamin-E deficiency, known to produce myocardial lesions in rabbits (Bragdon and Levine, 1949) and cattle (Gullickson and Calverley, 1946) might be worth investigating.

(2) *Humoral abnormality.*—The lesions in endomyocardial fibrosis are similar in nature to those seen in association with malignant carcinoid tumours. There is some evidence in both conditions that the fibrous endocardium results from organization of deposited fibrin thrombus. Humoral abnormality might therefore be a factor in endomyocardial fibrosis, as in carcinoidosis.

(3) *Sensitization.*—There are also similarities between the mural endocardial fibrosis I have described and the valvular endocardial fibrosis in rheumatic heart disease. This possibility of some pathogenetic relationship is strengthened by the finding of occasional cases which show lesions of both conditions. Though we are ignorant of the cause of rheumatic carditis there is reason to believe that the lesions are associated with sensitization to the products of streptococcal infection. Perhaps a similar mechanism is operating in endomyocardial fibrosis.

Another factor suggesting the possibility of sensitivity is the considerable eosinophilia which has been noted in almost all cases reported outside Africa. Cases in Uganda also show eosinophilia sometimes, but many of these also have helminth lesions, particularly dermal onchocerciasis, which itself causes eosinophilia.

(4) *Virus infection.*—Preliminary reports have described two varieties of virus myocarditis in Africa. One is from Johannesburg (Montgomery *et al.*, 1955) where an outbreak of Coxsackie virus myocarditis was seen in the infants in a maternity home. The other comes from the Belgian Congo, a region in which many of our patients had lived. Here small outbreaks of "encephalo-myocarditis" were thought to be caused by a psittacosis-like virus (Giroud and Jadin, 1955). Little morbid anatomy is available but 1 of the 3 fatal cases did show "l'endocarde . . . épaissi et sclereux". It would seem therefore that there are African viruses which can attack the human heart. Pearce of New York has produced myocarditis in rabbits with several viruses (Pearce, 1950). The resulting acute lesions include endocardial proliferation with obliteration of the crevices. These lesions have not been followed to the chronic stages but allowing for the difference in phase the similarity is remarkable. Other lesions include endo- and myo-cardial fibrosis and calcification. Pearce himself says our lesions resemble his, particularly those of his produced by the myxoma virus.

In conclusion, we do not know the cause, but several pieces of evidence seem to indicate a virus infection.

Other Obscure Heart Diseases in Africa

Novel and mysterious though this condition is, it is only one of a number of obscure varieties of heart disease described recently in different parts of Africa. Apart from the virus myocarditis mentioned there are:

(1) Post-operative mural thrombosis with death from heart failure and embolism described in Dakar by a group of surgeons (Letac *et al.*, 1952-53).

(2) "Nutritional heart disease" with heart failure sometimes responding to a good diet is described in Johannesburg by Gillanders (1951) and Higginson *et al.* (1952). These hearts also show mural thrombi.

(3) "Cardiac collagenosis" is the term used by Becker *et al.* (1953), also in Johannesburg, for a somewhat similar lesion which they believe to be a collagen disease.

(4) "Myocarditis": In Nigeria (Nwokolo, 1955), in South Africa (Higginson, 1952) and in Uganda, patients dying of heart failure are not infrequently found to have cellular infiltration of the myocardium for no apparent reasons. The cells vary, but in some cases eosinophils predominate.

It would seem that for cardiologists as for explorers in other fields, Africa is maintaining her reputation as the source of the new and unexpected.

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Primary Amyloidosis

By R. I. S. Bayliss, M.A., M.D., F.R.C.P.
Assistant Physician, Westminster Hospital, London

In surveying this curious condition of primary amyloidosis I have drawn heavily on the excellent reviews by Matthews (1954) and by Symmers (1956)—this last providing an unsurpassed description of the pathological findings.

Classification.—Amyloidosis has been classified into primary and secondary types. As Symmers (1956) has pointed out, however, it is a common misconception that primary amyloidosis implies a particular and unusual distribution of amyloid different from that found in secondary amyloidosis; that the material presents anomalous staining reactions, and that the disease has a characteristic clinical picture. This may be true in some cases but often the distribution and tinctorial reactions of the amyloid tissue may be very similar in the primary and secondary types, so that a pathologist examining histological material without prior knowledge of the case may be unable to predict whether or not the patient had any other precipitating disease. The distinction between primary and secondary amyloidosis resides solely in the fact that secondary amyloidosis is associated with some other disease, presumably important from the ætiological point of view, whereas in the primary type there is no apparent precipitating condition. This distinction is important because correction of the underlying disease may cause a considerable regression in secondary amyloidosis while no effective treatment for the primary type has yet been evolved.

The simplest classification is:

(1) Secondary amyloidosis (associated with some primary disease such as chronic suppuration, rheumatoid arthritis, myelomatosis, Hodgkin's disease, syphilis).

(2) Primary amyloidosis.

(3) Localized amyloid tumours. (These tumours may be localized to the bladder, the upper respiratory tract or the intestines. In some patients an extensive pathological search will reveal clinically silent areas of amyloidosis in other organs and such cases are really examples of systematized primary amyloidosis.)

Pathological findings.—In primary amyloidosis almost any organ of the body may be involved. In the majority, however, there is maximal involvement of the heart and striated muscles, and less striking affection of the liver and other visceral organs. This is in contrast to the findings in most cases of secondary amyloidosis where the brunt of the disease tends to fall on the abdominal viscera. The staining reactions of the amyloid material in both primary and secondary amyloidosis are unpredictable with regard to Congo red and the metachromatic stains such as methyl violet. Although the affinity for Congo red is usually more marked in secondary than primary amyloidosis this is not always so, and often there is a difference from one organ to another. Van Gieson's stain is of value in cases where the amyloid tissue fails to stain with Congo red or methyl violet: the amyloid material takes on a peculiar khaki colour, stands out from the surrounding background and is readily distinguished from hyalinized collagenous tissue.

Clinical manifestations.—The commonest clinical presentation of primary amyloidosis is cardiac failure and this has been the method of presentation in about half the reported cases (Dahlin, 1949; Wollaeger, 1950). Since the average age of patients with primary amyloidosis is 55 years, it is not surprising that the ætiology of the cardiac failure is attributed to hypertensive or ischæmic heart disease. In only a few instances has the correct diagnosis been made *ante mortem* when there have been other features to suggest primary amyloidosis, but the condition should be suspected when there is cardiomegaly without evident cause. The electrocardiogram usually shows low voltage QRS complexes and iso-electric or diphasic T waves in all leads but there is nothing characteristic or specific. The response to digitalization and mercurial diuretics is often poor, and the patient usually dies in a matter of months.

The second most common method of presentation is involvement of striated muscle, and the organ usually affected is the tongue. About a quarter to a third of patients with primary amyloidosis present with macroglossia. The base of the tongue is more involved than the anterior part, and the infiltration may extend, as in one of our recent patients, to the laryngeal and hyoid muscles (Bayliss, 1957).

Involvement of more peripheral muscles is clinically less obvious but may explain the muscular weakness experienced by many patients.

In a quarter of the patients skin lesions occur. The most common manifestations are purpura and small ecchymoses which should be carefully sought for, especially on the eyelids. More specific are amyloid deposits in the skin and subcutaneous tissue. Sometimes the finger pulps are enlarged clinically, but even if they appear normal a biopsy from this site may confirm the diagnosis.

In a small proportion gastro-intestinal symptoms predominate. Thus on three occasions amyloid infiltration of the stomach has led to an erroneous diagnosis of carcinoma ventriculi, and other patients have presented with gastro-intestinal bleeding, and constipation or diarrhœa. Involvement of the liver is more common in secondary amyloidosis, but some patients with the primary type present with hepatomegaly, and develop ascites. Cirrhosis or hepatic metastasis is usually suspected. Tests of liver parenchymal function are normal, and the true diagnosis may be suggested by finding cardiomegaly or involvement of the tongue or by hepatic biopsy.

Other clinical presentations include the nephrotic syndrome, lymph-node enlargement, peripheral neuritis and enlargement of the thyroid. A patient now under the care of Dr. S. P. Meadows at Westminster Hospital presented with a most painful peripheral neuritis, oculomotor pareses, and generalized lymph-node enlargement. The diagnosis was confirmed by biopsy of a lymph gland. Subsequently he has developed hepatomegaly and ascites, and evidence of adrenal insufficiency. Very occasionally a familial history of primary amyloidosis is obtained. Neurologists in Portugal have described families with amyloid peripheral neuropathy, and other familial cases have been recorded in the United States.

Amyloidosis in association with myelomatosis.—About 15% cases of myeloma develop amyloidosis (Bayrd and Bennett, 1950) which may have more of the features usually found in primary rather than secondary amyloidosis and be associated with intra- or extra-osseous amyloid tumours. Occasionally the amyloid material is even found in the cytoplasm of the plasma cells. There does not seem to be any correlation between the development of amyloidosis and the presence of either Bence-Jones proteinuria or hyperglobulinæmia.

Diagnosis.—Confirmation of the diagnosis is best obtained by biopsy. The site for this may be clinically obvious but must in the case of the tongue contain muscle tissue and should be sited as far away from the tip as possible. Where only the heart is clinically involved biopsy of the liver by hepatic puncture or of a finger tip may be rewarding.

The intravenous Congo red test is worth carrying out, particularly if the technique suggested by Fearnley and Lackner (1955) is used, but negative results are often obtained even when there is extensive infiltration.

Prognosis.—The outlook is always bad; death usually from heart failure occurring within two years.

Treatment.—Although there is evidence of reversal of secondary amyloidosis when the ætiological condition is successfully treated, no convincing improvement has been obtained in the primary condition. Claims have been made that large doses of liver extract and massive doses of ascorbic acid cause improvement. The uptake of Congo red may be influenced by these measures, but it is doubtful if the underlying metabolic disturbance is changed. In some cases of macroglossia surgery has been undertaken to make the patient's plight more tolerable. Thus in one case Sir Stanford Cade (Weber *et al.*, 1937) did a successful wedge resection of the tongue but the patient died eight months later of cardiac failure.

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BOOK REVIEWS

Diseases of the Liver. Edited by Leon Schiff, M.D., Ph.D. (Pp. xix + 738; illustrated. £5 10s. 0d.) London: Pitman Medical Publishing Co. Ltd. 1956.

This finely-produced book has been written by a team of experts, some of whom work in this country although most are centred in various parts of the United States of America. The foreword points out that the writing of separate sections on one organ by over a score of different authors might well be regarded as ultra-specialism at its most advanced. That this is not so the reader will soon discover when he recognizes how comprehensive is the outlook of most of the contributors, and how the book, although taking a single organ as its main theme, covers a very large part of general medicine.

It is arranged in the well-established manner, beginning with anatomical, physiological and biochemical considerations, and passing on to methods of investigation before describing disorders of function.

All these preliminary sections are excellent, have been clearly written and illustrated by explicit diagrams and some remarkably good photomicrographs.

Emphasis is laid on the experimental method as applied to hepatic disorders, and a section is devoted to experimentally induced hepatic injury, further mention being made of this approach by Sherlock in her section on the liver in congestive failure.

The discussions of disorders of the liver which follow pay full attention to the major problems, and in particular to those of pathology. They cover their respective fields in an up-to-date and authoritative manner, and are, withal, readable. Their value is much increased by the very ample bibliography which is given at the end of each section, reference being made to between 400 and 500 publications in one instance.

A search for minor points or rarer conditions is made easy by the high quality of the index, and is rewarding as the information is there to be found. The hepato-toxic effects of Chlorpromazine are an example of a short, clear account, which is, nevertheless, up to date and full.

This is an attractive book to handle and will prove an invaluable reference book to many, since by elective use the student, the practitioner, consultant or specialist will find, in most instances, that which he is seeking.

Pulmonary Circulation and Respiratory Function. A Symposium held at Queen's College, Dundee. (Pp. xii + 44; illustrated. 12s. 6d.) University of St. Andrews. 1956. (Distributed by E. & S. Livingstone Ltd., Edinburgh and London.)

The Faculty of Medicine of the University of St. Andrews, "conscious of the sad walls that bound the specialties", brought together in Dundee last autumn a distinguished body of people with a common interest in the working of the lungs. The 126 members of this symposium included physiologists, surgeons, physicians, pathologists and at least one obstetrician. No less than one in five of these is the occupant of a University chair, including Professor Liebow of Yale, whose visit as Praelector in Pathology to St. Andrews provided the stimulus for this venture. The proceedings at the two-day meeting are now published in a slim and attractive volume in which the papers given by the twelve principal speakers and the 27 contributions to the discussion are fully reported and illustrated. The book is divided into two parts: "The Pulmonary Circulation in Health and Disease" and "Respiratory Function". There is no doubt that the pulmonary circulation was intended as the main theme of the symposium and the lively discussion of this subject itself justifies the purchase of the book.

The selection of papers in the second part is not as well balanced as in the first. There is a brief general review of respiratory function tests, two papers describing various types of mechanical respirators, one dealing with gas diffusion in the lung and a fifth with pulmonary function in the newborn lamb. The ventilatory aspects of lung function are only briefly discussed and few of the important recent advances in the study of mechanical function are mentioned. The organizers may possibly have felt that accounts of this more specialized work would not have encouraged the broad discussion which was so valuable a feature of the symposium. Those who remember the autumn meeting in Dundee will not be surprised by the fine quality of this publication.

Pathologic Physiology: Mechanisms of Disease. Edited by William A. Sodeman, M.D., F.A.C.P. 2nd edition. (Pp. xxx + 963; illustrated. 91s.) Philadelphia and London: W. B. Saunders Company. 1956.

This is a fascinating book, compiled by 29 American authorities, many of whom are almost as well known in Great Britain as in the U.S.A. The thirty-one different chapters cover all the various systems of the human body, with special chapters relating to such subjects as genetics of abnormal growth and neoplasia, carbohydrate metabolism, water and electrolyte balance, infection and allergy.

The system adopted throughout the book is to give a short account of the anatomy of the part under review, followed by a detailed account of the physiology and histology, with especial reference to such mechanisms as are important to the clinician. Then later in the chapter, or in the chapter immediately following, is an account of the principal clinical states or diseases. Nowhere have we previously found such a composite description of the physiological and pathological mechanisms in diseased conditions.

The book is not one that should be read *in extenso* by an undergraduate medical student, but post-graduates reading for higher degrees and diplomas will find it of great help. It seems unfair to be too critical in relation to a book of this excellence; but we would suggest that the index could be usefully expanded, and the number of diagrams added to by figures illustrating, for example, the electro-cardiographic changes in potassium deficiency. Perhaps also in a future edition the chapter on the central nervous system, and such descriptions as that of electro-encephalography, could be usefully expanded. These criticisms do not, however, greatly detract from what can be regarded as a most useful and well-produced textbook, and the clarity of the print adds to the general enjoyment.

Old Age in the Modern World. Report of the Third Congress of the International Association of Gerontology, London, 1954. (Pp. viii + 647; illustrated. 35s.) Edinburgh and London: E. & S. Livingstone Ltd. 1955.

This report of the Third Congress of the International Association of Gerontology held in London in July 1954 has been published by the British Organising Committee.

Realizing the impossibility of publishing the verbatim report of the Congress the Editorial Committee, entrusted with this task, gave "preference to communications containing original material, opening up new avenues of thought, or presenting authoritative reviews". Other material is given in abridged form or referred to by title only.

For historical record the verbatim report has been deposited with the Library of the Royal Society of Medicine.

The Editorial Committee: Dr. C. Boucher, Dr. O. Olbrich, Mr. W. A. Sanderson, Dr. J. H. Sheldon, Professor R. E. Tunbridge and Dr. Marjory W. Warren, may be truly congratulated on the results of their work. In "Old Age in the Modern World" the reader will find information tackling almost every aspect of the problem of old age, be it administrative, medical or social. From the enormous material of the Congress the Editorial Committee selected the most valuable and original work and assembled this in such a way as to help the reader to find easily the subject in which he is most interested.

The book starts with the speech given at the opening session of the Congress by the Minister of Health, the Rt. Hon. Iain McLeod, M.P. It is followed by the Public Oration delivered by Miss Margery Fry and the Presidential Address by Dr. J. H. Sheldon on "The Social Philosophy of Old Age".

The report itself gives original papers assembled in seventeen chapters dealing with administrative, biochemical, clinical and social aspects of old age in various countries of the world. It gives a good picture of differences in the social structure of populations in other countries and of different methods adopted to deal with the problems of old age. It discusses the results of original surveys on accidents, employment, performance and training in relation to old age.

Throughout the report there is a deep understanding that the aspects of the problem of old age, social and medical, influence each other and cannot be separated. There is also an appreciation that in order to achieve success in dealing with these problems team work is needed and this applies equally whether it be work including planning on a national scale or work in a hospital ward. The fact that old age has its privileges, but has also its responsibilities is constantly referred to. These are some of the common trends flowing through the pages of this book.

It is obvious from the report that more and more people are conscious of the problems of old age and of how they affect every aspect of life.

I consider the report to be a very encouraging one, especially for those who for years now have been engaged in a rather lonely and unspectacular fight for the needs and rights of old people.

Pædiatrics for the Practitioner, Supplement 1956. Under the General Editorship of Wilfric Gaisford, M.D., M.Sc., F.R.C.P., and Reginald Lightwood, M.D., F.R.C.P., D.P.H (Pp. 116 + index 10 pp.; illustrated. 32s. 6d.) London: Butterworth & Co Publishers Ltd. 1956.

This supplement is divided into two parts, the first part containing original articles, and the second part being called a Noter-up.

In the first part there is a chapter that deals with physical changes of puberty and adolescence, and contains a good diagram in relation to the endocrine control of sexual development. Owing to the complexity of the subject and the rapid increase in the biochemical knowledge of the structure of the hormones, the author is unable to lay down a detailed plan for the management of the variations in sexual development around puberty, so that the general practitioner will be forced to send the child to the endocrine clinic when the parents become alarmed.

The chapter on care of children in the tropics is introduced by a good account of advice that can be given to European parents who are going to settle abroad with their children. Then follows an account of the cosmopolitan diseases that may be encountered in the tropics, which includes the bacterial and virus diseases. There is a good account of amœbic dysentery and its complications, followed by an account of trypanosomiasis as it occurs in Africa and South America. This is followed by a complete account of tropical disease as it occurs in childhood.

The general practitioner will find this chapter of great value as a form of reference now that so many coloured children are entering this country from abroad.

The second part of this supplement is headed "Noter-up" and consists of additional information, in relation to the text of the three volumes of Pædiatrics, but it also contains what one would term "corrections" in the light of new knowledge.

I think it would have been better to have placed the additional information under the heading of a supplement, and the small corrections could have come in leaflet form in relation to Volumes I, II and III. On the other hand the Noter-up does keep the three volumes of Pædiatrics well up to date, and as the years go by can be contained in a small volume entitled "Pædiatrics 1957".

The 1956 Supplement is clearly and well written and brings the three volumes of Pædiatrics up to date.

Principles of Biochemistry: an integrated presentation of fundamentals. By A. White, Ph.D., P. Handler, Ph.D., E. L. Smith, Ph.D., and D. Stetten, Jr., M.D., Ph.D. (Pp. vii + 1117; illustrated. £5 12s. 6d.) New York, Toronto and London: McGraw-Hill Book Co., Inc. 1954.

The first thing to say about this work is that it is probably the best advanced textbook of biochemistry at present available. For the postgraduate student who is already specializing in biochemistry, or for the research worker, or for the medical man who wishes to have access to up-to-date information about (shall we say) the aberrant metabolism characteristic of a particular disease—this is assuredly the first volume to consult. Running, as it does, to over eleven hundred pages, it is no doubt a little too deep, and perhaps a little too recondite, for the elementary student of medicine, or for the average practitioner who, unhappily, may not feel himself sufficiently familiar with the complex theoretical bases of modern biochemistry, in thermodynamics, in the electronic theory of valency, or in the niceties of stereoisomerism. But, for those who need a thorough and a scientific treatment, this text may very well form the introductory reading of their choice, before in turn they proceed to even more specialized monographs. The reader can be sure of a critical appraisal of current teaching, and he will find, in some sections, a brief and well-balanced summary of contemporary research. Throughout, primary consideration has been given to the applications of biochemistry in its relations to the mammalian organism, and particularly to man; however, the problems of comparative biochemistry, including microbiology, are by no means excluded.

The "integrated presentation of fundamentals" at which the authors have aimed, although achieved in a remarkably novel way, has certainly been an unqualified success. The procedure that they adopted to write this book was as follows. The first draft of each chapter was assigned to one of the four authors, and when completed was criticized by the other three. Then the four authors met at intervals for discussions of several days' duration; and in some instances the material already written by one author was rewritten by another. Thus, in the end, all four authors had assumed responsibility for, and had in fact contributed to, each chapter. In consequence, the faults not infrequently associated with books written jointly by several authors, such as overlapping and unevenness of style and treatment, are here conspicuous by their absence.

Human Pathology. By Howard T. Karsner, M.D., LL.D. 8th edition. (Pp. xxiv + 960; illustrated. £6.) London: Pitman Medical Publishing Co. Ltd. 1955.

This book has now reached its eighth edition in a period of twenty years and this new volume has been brought thoroughly up to date. It is divided into two parts: part I occupies 380 pages and sets out in simple language the general phenomena of pathology and

the factors which are concerned with it. Part II is termed Systemic Pathology and deals with the various diseases as they affect the different systems of the body.

The contents of the book are well produced and are illustrated by numerous reproductions of specimens and microscopic photographs. It has been brought up to date by the inclusion of much new material—incorporating present-day knowledge on such diverse matters as the blood pigments, the influence of cortisone and ACTH on pathological processes, the stress syndrome, toxoplasmosis and the viruses: and the section on diseases of the liver and of the nervous system have, in particular, been extensively revised. It is helpful to have the pathological phenomena so closely linked in a textbook with the principal clinical features and this to a student of Medicine, whether he be an undergraduate or a postgraduate, is a particularly attractive feature.

Altogether this is one of the best textbooks on pathology now in existence. Added to other attractive features is the excellent way in which the book has been produced and the clear print which makes it easy to read.

The Inquisitive Physician. The Life and Times of George Richards Minot, A.B., M.D. By Francis M. Rackemann, A.B., M.D. (Pp. xi + 288; illustrated. 40s. 0d.) Harvard University Press. London: Cumberlege. 1956.

This is one of the best medical biographies of recent years. Written by his cousin and fellow-student, it tells the story of a distinguished physician and scientific pioneer and at the same time paints a colourful picture of medical Boston in the last fifty years. The author's style is delightful, chatty, and extremely readable, and though the presentation is leisurely, we never lose sight of the principal character of the book. We are introduced to Minot's famous teachers at Harvard Medical School: Walter B. Cannon, the physiologist, Otto Folin, the biochemist, William T. Councilman, the pathologist, Henry A. Christian, the physician, Theobald Smith, the comparative pathologist, J. Homer Wright of "Wright's stain"; at Johns Hopkins where Minot went for postgraduate studies we meet William Sidney Thayer, Alan M. Chesney, and William H. Howell. In 1921 at the age of 35 Minot developed severe diabetes which was treated by Dr. Elliott P. Joslin. Fortunately for the patient and fortunately for all the patients in the world with pernicious anæmia, insulin was then discovered; otherwise Minot would not have lived to make that great contribution with which his name will forever be linked. It was in August 1922 that Banting and Best had sufficient insulin to send a small sample to Joslin. One of the most interesting chapters in the book is naturally devoted to pernicious anæmia (1926), and another chapter tells how the discoverer of liver treatment was awarded the Nobel Prize for Physiology and Medicine in 1934 jointly with William P. Murphy and George H. Whipple. The man behind the scientist is skilfully and sympathetically sketched: Minot bristling with intellectual curiosity; Minot the absent-minded professor; Minot always writing notes whenever he had an idea—"about once every hour or so"—on the edge of an advertisement torn from a magazine; Minot practising the art of courageous living. The book concludes with a genealogy, references, and a good index.

Physical Diagnosis. By Ralph H. Major, M.D., and Mahlon H. Delp, M.D. 5th Edition. (Pp. xi + 358; illustrated. 49s. 0d.) Philadelphia and London: W. B. Saunders Company. 1956.

In the fifth edition of this manual Dr. Ralph H. Major, Professor of Medicine and of the History of Medicine in the University of Kansas, is joined by Dr. Mahlon H. Delp as co-author. The book follows the teaching of the great Skoda that physical signs are produced by physical causes which must be understood before the signs can be properly appreciated. The text is sound and practical, and it is lavishly illustrated by photographs, diagrams, charts, and tables. Some of the illustrations, though well chosen, are not reproduced too clearly, and a few seem unnecessary, but the majority are excellent, and of them it may properly be said that every picture tells a story. It is pleasing to come across a number of original illustrations used by the pioneers in the art of physical diagnosis. Throughout the book there is a delightful historical undercurrent exemplified by numerous "asides" and by the free use of classical descriptions. Priority claims are carefully, but not pedantically, noted. It is regretted that in many cases surnames only are given. In the section on temperature there is no mention of Carl Wunderlich of whom it has been said that he found fever a disease and left it a symptom. Each chapter concludes with a short bibliography, and there is a 30-page index. This fifth edition which has been extensively revised and enriched by many new illustrations, will be found useful and refreshing by the medical student, the practitioner, the teacher, and the consultant. The wealth of pictures makes the price seem moderate.

Transactions of the American Ophthalmological Society 1955. Ninety-First Annual Meeting West Virginia 1955. Being Volume LIII of the Transactions of the Society. Edited by Dr. Gordon M. Bruce. (Pp. xix + 522; illustrated. 144s.) Columbia University Press. London: Cumberlege. 1956.

The 53rd Volume of the "Transactions of the American Ophthalmological Society" presents 19 papers and 3 theses. Some of them are of interest to the physician—blindness following hexamethonium, tuberous sclerosis and retinal findings, periarteritis nodosa and corneo-scleral lesions; some are of interest to the neuro-surgeon—a study of 119 cases of intracranial aneurysm, fibrous dysplasia affecting the periorbital region; but most are specialized and technical. In spite of the spate of literature which has appeared since the war on glaucoma, there are seven papers on various aspects of this disease and its treatment; most of them original in content.

Each paper is followed by a discussion, the opener of which is present by invitation and has read the main paper before the meeting. This makes for informed criticism and facilitates considerably an understanding of the subject. The whole is a tribute to the vitality of American Ophthalmology.

The Royal Northern Hospital 1856–1956. By Eric C. O. Jewesbury, M.A., D.M.Oxon., M.R.C.P. (Pp. xi + 157; illustrated. 17s. 6d.) London: H. K. Lewis & Co. Ltd. 1956.

Seldom can it have happened that "Pygmalion language" plus a slap on the buttocks of an anæsthetized patient has benefited humanity as a whole, and the people of North London in particular. Yet it was undoubtedly the uncouth behaviour of Sherard Freeman Statham, Fellow of the Royal College of Surgeons, which led directly to the foundation of the hospital, now known as the Royal Northern Hospital.

It was also, of course, the inability of the University College Hospital Council to judge Statham's real character which led them to dismiss him from their honorary staff.

Most people now realize that the surgeons of his generation were pioneers in surgery and it was the strain of this pioneer work which made them seem so uncouth, and that they tried to overcome and hide their own nervousness by assuming this blunt manner. Their criticism of the theatre staff and assistants while operating was really self-criticism. The author mentions Lockwood in this connexion, and a story is told of Victor Horsley, who called his theatre sister a " B—— fool" during an operation, met her the next day and, having forgotten the incident, congratulated her on the way everything went.

There was some excuse for these pioneers, but there was no excuse for the next generation, who, without being pioneers, copied the manners of their seniors. All this soon died out and we came to the generation of Barrington Ward, who, as the author mentions, will long be remembered not only for his professional skill but for his great courtesy. If the phrase were not outmoded Barrington Ward could be described as an example of the perfect gentleman.

Much of this history related is a terrible struggle to find money to run the hospital, and Statham spent what little money he had on this great enterprise. When he died of tuberculosis at the age of 32 he left less than £600.

One of the people who did so much for the hospital was Gilbert Panter, secretary for forty-two years. This man just lived for the hospital and on two occasions his services were publicly recognized with special ceremonies, and deservedly so.

In 1948 the hospital was taken over by the National Health Service.

The history of this hospital describes a long struggle for an ideal over a period of one hundred years. The struggle for money is over, but the struggle to give the public the most up-to-date and best treatment and service continues.

This history so brilliantly written by Dr. Jewesbury will interest all those who, like the writer, have had the privilege of serving on the staff of the hospital, and many others; it will also serve as an inspiration to coming generations.

Subarachnoid Hæmorrhage. By John N. Walton, M.D., M.R.C.P. Foreword by Sir Charles Symonds, K.B.E., C.B., D.M., F.R.C.P. (Pp. xv+350; illustrated; 30s. 0d. Edinburgh and London: E. & S. Livingstone Ltd. 1956.

The author is to be congratulated on producing a valuable work of reference upon subarachnoid hæmorrhage, a subject which has become of increasing importance now that the underlying lesions are better known. It is fitting that the foreword should have been written by Sir Charles Symonds who some thirty years ago made a major contribution to our knowledge of subarachnoid hæmorrhage. The clinico-pathological study of this subject is essentially an achievement of modern neurology and is an indication that this discipline is by

no means exhausted and that there yet remain for the alert clinician opportunities of making notable contributions to diagnosis and to treatment.

The monograph is based upon the analysis of 312 particular examples of subarachnoid hæmorrhage together with a review of the extensive literature on the subject. It is well written and arranged, and gives an admirable critical discussion upon treatment. The task of the reader would be made a little easier if every chapter were not infiltrated by figures of a statistical order. Statistics have their necessary place in a work of reference, but it is surely unnecessary that the important sections describing the clinical picture and course and their relation to the several lesions involved should everywhere tell us how many times this and that sign or symptom was present or absent in the total of cases reviewed.

Subject to this minor criticism, the monograph may be strongly recommended as an interesting and comprehensive account of its subject.

Diagnosis and Treatment of Vascular Disorders (Angiology). Ed. by Saul S. Samuels, A.M., M.D., F.A.C.A., F.A.C.C. (Pp. x+622; illustrated. 128s. 0d.) London: Baillière, Tindall and Cox. 1956.

The Chief Editor of this work states that while the blood vessels are considered part of the cardiovascular system our knowledge of them in health and disease has so expanded as to require the entire attention of any single physician or surgeon; in fact he makes a case for separating a specialty of angiology from the comprehensive one of cardiology. Apart from Dr. S. S. Samuels, sixteen other workers contribute to this book which deals with the anatomy and physiology of the peripheral circulation and the diagnosis and treatment of the several diseases that may affect it; three authors write a chapter each from the Department of Surgery in Manchester University, Professor R. H. Goetz of Cape Town University has contributed five chapters, and American workers in this field are responsible for the remaining 16 chapters. Naturally, with such a strong team the book comprises an exhaustive study of the subject, and no one who is specially concerned with the diagnosis and treatment of vascular disorder should be without it although admittedly it is expensive. None the less the price is not too high for a book whose leaves in art paper show so many faultless illustrations, and such authoritative information on a newer section in medicine.

Pott's Paraplegia. By D. Ll. Griffiths, H. J. Seddon and R. Roaf. (Pp. xiv+129; illustrated. 50s.) Oxford University Press. London: Cumberlege. 1956.

Every surgeon or physician who deals with spinal tuberculosis should have this volume on his bookshelf, or preferably on his desk. This monograph reviews the clinical features and pathology of Pott's paraplegia, states the need for operative interference and gives the results of the operations which have been practised. The authors establish their thesis that, in general, operative decompression is the most effective treatment of severe paraplegia, and that in the thoracic region, antero-lateral decompression surpasses other techniques. The results of conservative treatment are critically assessed and found wanting.

Antero-lateral decompression in 50 cases of failed conservative treatment produced 36 successes (the standard of success being either complete neurological recovery beginning immediately after the operation, or recovery of ability to walk well, this recovery commencing during the early post-operative period).

The operation of antero-lateral decompression is so beautifully and clearly described, and made to appear so simple, that the authors are wise to give a final word of advice that its performance should be restricted to experienced spinal surgeons, with intimate knowledge of the conservative treatment of spinal tuberculosis, working in centres fully equipped for the management of the disease and for difficult surgery.

With its 30 plates and 26 diagrams and figures, and with its clarity of exposition, this book is a shining example of how a monograph on any subject should be presented.

The Support of Medical Research. A symposium organized by the Council for International Organizations of Medical Sciences. Edited by Sir Harold Himsworth and J. F. Delafresnaye, C.I.O.M.S. (Pp. xi+170. 17s. 6d.) Oxford: Blackwell Scientific Publications. 1956.

In October 1954 the Council for International Organizations of Medical Sciences (established under the joint auspices of UNESCO and WHO) conducted a symposium "The Support of Medical Research" at the Royal Society of Medicine. This was an historic occasion, for though in the last fifty years central research organizations of medical sciences have been created in a number of countries, their directors had never been given the opportunity of meeting their colleagues collectively and of comparing their experiences. Those who attended this conference will welcome the publication of its report in so pleasant and informal a

volume, to refresh their memories as well as themselves. But anyone interested in medical research should study this report carefully. Its contents include a list of participants; the opening remarks by the chairman, Sir Harold Himsworth; and the report on the conference under the headings: universities and medical research, functions and structure of central research organizations; support of medical research by a central organization; grants; research units and institutes; co-operation between universities and a central research organization; recruitment, training, and support of medical research workers; collaboration in research. Appendices deal with medical research in Australia, New Zealand, Canada, Union of South Africa, Republic of Ireland, India, U.K., U.S.A., Belgium, France, Switzerland, Germany, Netherlands, Scandinavia, Yugoslavia, and Israel. It is significant to note that some countries experience difficulty in recruiting research workers in the pre-clinical fields because of low salaries. The volume concludes with a carefully compiled bibliography (volume numbers of such periodicals as the *British Medical Journal* and the *Lancet* should be given in Roman numerals) and with an index.

Landmarks in the History of Hygiene. By Henry E. Sigerist, M.D., D.Litt., D.Sc., F.R.C.P. (Pp. xii+78; illustrated. 12s. 6d.) Oxford University Press. London: Cumberlege. 1956.

In founding the series of lectures bearing his name and delivered annually at the London School of Hygiene and Tropical Medicine, George Heath Clark emphasized that they should be concerned with the historical, cultural and philosophical aspect of public health. Few are as well fitted to cover these fields as the author of this volume, Dr. Henry Sigerist, the medical historian. Like all his writings, these lectures betray that universality of interests and learning which makes for distinction in a subject where the correlation of different disciplines is basic.

Although some might consider Hippocrates as much the father of hygiene as of clinical medicine, Dr. Sigerist chose Galen as his first subject, pointing out that, as the physician to the Roman court, he was concerned more with the pursuit of personal health by a leisured class than with community hygiene as we understand it to-day. The Regimen Sanitatis of the Salerno school, which reflected this viewpoint, is discussed in some detail. Personal longevity continued to be the aim of the educated laity during the Renaissance and there is a vivacious discussion of the recommendations of Cornaro which were designed to ensure it. His golden rule—to eat just enough "to keep body and soul together"—is receiving fresh backing from recent work on the atherogenic properties of fat in the diet.

With Johann Peter Frank came a change in emphasis. His term for medical officers of health (medizinischen Polizei) has an unpleasant ring to-day but his conception of them as guardians of the community's health was essentially sound. Poverty as a cause of disease and a bar to treatment led to the development of schemes of medical care by, of all apparently unlikely people, Bismarck, and Dr. Sigerist ends his series of lectures with a balanced account of the changing pattern of medical care and some personal thoughts on its future. It is good that these lectures will now reach an audience which may be larger than the original one but is unlikely to be more appreciative.

Radiology of the Alimentary Tract in Infancy. By Roy Astley, M.B., M.R.C.S., D.M.R. (Pp. viii+287; illustrated. 50s.) London: Edward Arnold (Publishers) Ltd. 1956.

The high quality of pædiatric radiological practice at the Children's Hospital in Birmingham has become an established tradition and is widely known. Dr. Roy Astley is to be congratulated on the production of a most valuable book which fully maintains this high tradition. His book is the outcome of exceptional experience and interest in the problems of alimentary disease in infancy and the greater part of the book is clearly based directly on his personal observations.

In a modestly composed preface, the author states that many chapters conclude with illustrative case histories, chosen to emphasize points that have been made in the general text; these are presented in a different type so that for quick reading they may be omitted if desired. This is certainly not a book which merely deserves quick reading: in the reviewer's opinion these case histories are an invaluable feature of the book and should be read thoroughly.

The sections on hypertrophic pyloric stenosis and duodenal obstructions are particularly well done. The general quality of the radiographic illustrations is excellent, especially when it is remembered that co-operation from infant patients is non-existent.

This book should be read by all radiologists and pædiatricians and should be available for quick reference in all radiological departments to which an acutely ill infant may be referred.

Soranus' Gynecology. Translated with an introduction by Owsei Temkin, M.D. (Pp. xix + 258; illustrated. 40s. 0d.) Baltimore: Johns Hopkins Press. London: Cumberlege. 1956.

Soranus, who lived in the early second century A.D., was one of the most learned and critical writers of antiquity. Though the majority of his works have been lost, his most important book, "Gynecology," which exerted considerable influence on many generations both in the East and the West, has been preserved in the original Greek. It is an interesting and historically important document, representing ancient gynæcological and obstetrical practice at its very height, and written apparently for the physician, the midwife, and the educated layman. It has now been translated for the first time into English by Dr. Owsei Temkin, Associate Professor of the History of Medicine at Johns Hopkins University and editor of the *Bulletin of the History of Medicine*, with the help of two obstetricians, Drs. Nicholas J. Eastman and Alan F. Guttmacher, and of a classical scholar, Dr. Ludwig Edelstein. In a fascinating and erudite introduction Dr. Temkin tells the inside story of the translation which was begun some twenty years ago; depicts Soranus as the outstanding representative of the methodist school that derived its knowledge from studying the phenomena of disease; discusses the scope, merits, and weaknesses of the "Gynecology"; and gives an account of the various texts and editions.

The "Gynecology" consists of four books. The first deals with midwives, menstruation, virginity, conception, abortives and contraceptives; the second with parturition and the care of the newborn (a particularly enlightening section); the third discusses various gynæcological conditions (e.g. "hysterical suffocation, "flux of semen" in women), their pathology and treatment, but the author's ideas on the whole strike us to-day as antiquated and vague. The final obstetrical book, on the other hand, is valuable and much more modern. The volume concludes with a list of Ancient Names, Materia Medica (the botanical terms are difficult to identify, especially as Soranus gives no descriptive details), and an Index of Personal Names and Subjects.

Gynæcologists, obstetricians, pædiatricians, and medical historians owe Dr. Temkin a great debt for his labour of love in making this important work available to them in so scholarly and sympathetic a translation which carefully avoids forced interpretations in the light of present-day knowledge, and for his excellent introduction. Their thanks are due also to the Johns Hopkins Press for producing this beautifully printed book—a publication of the Institute of the History of Medicine—which it is a joy to read.

Management of Life-Threatening Poliomyelitis—Copenhagen, 1952–1956. Edited by H. C. A. Lassen, M.D. (Pp. xi+179; illustrated; 22s. 6d.) Edinburgh and London: E. & S. Livingstone Ltd. 1956.

The names of Dr. Lassen and his colleagues became world famous for their magnificent feat of improvisation in the Copenhagen epidemic of 1952. This book is in many ways a history of this epidemic and as such is a most thorough and complete analysis. The statistical tables cover every conceivable feature of the epidemic. Naturally as a textbook it suffers, in some degree, from this historical viewpoint and we might perhaps feel that we had advanced farther in this country. Only Scandinavian machines and methods are described, and of the former we have had somewhat unfortunate experience. There is an attempt to segregate cases into distinct types which we have found seldom applicable. The chapters on basic mechanics of ventilation are quite excellent and indications for tracheotomy are well portrayed. Strangely there is no mention of preliminary "trial" laryngeal intubation. The operation of tracheotomy is well described, but it is not emphasized that a ring of trachea must be left above the stoma. This may account for some space being devoted to the cure of laryngeal stenosis.

The chapters on laboratory procedure are excellent, though perhaps indicating complete reliance on such findings whereas we, apparently, have more faith in clinical judgment.

The discussion of metabolic disturbances in acid-base balance are a little obscure but may have suffered in translation.

In discussing calculus formation it would seem that urinary pH followed a post-prandial pattern, rather than correlation with volume of ventilation, and thus that urinary pH is not a good guide to oxygenation except in extremes of over- or under-ventilation.

This book written on a fast-developing subject is inevitably somewhat behind current practice. It does, however, give a detailed picture of the problem to be faced and contains a mass of information on every aspect of respiratory poliomyelitis. Above all it is a fine record of the achievement of the Copenhagen School when faced with the crisis of 1952.

Cancer Cells. By E. V. Cowdry. (Pp. xvi+677; 137 figs. 112s.) Philadelphia and London: W. B. Saunders Company. 1955.

The purpose of this book, as the author states in the Preface, "is to introduce the reader to the more important facts about cancer cells, to raise questions considered important and, whenever possible, to supply clues as to how he can further explore the issues for himself."

The book develops logically from a definition of cancers in Chapter 1 and a description of the nature of malignant growth in Chapter 2 to consider the cytoplasm and nuclei of normal and malignant cells in Chapters 3 and 4, the chemical properties of cancerous tissues in Chapter 5 and the occurrence of cancers in animals and plants in Chapter 6. In Chapters 7 to 10 the author discusses agents which cause cells to become malignant, and the role of single injury, of viruses and of mutation. Chapters 11 to 13 deal with cellular susceptibility to cancer and with the part played by heredity, by age and by sex. The next three chapters review the subjects of latency and of modifying factors in cancer development and the geographic frequency of different types of cancer. Chapters 17 and 18 deal with prevention, diagnosis and treatment, and Chapter 19 with unexplained disappearance of cancer cells. The last chapter reviews the whole field of cancer research and probable future developments. The book ends with an appendix giving among other things a list of journals, reviews, books, conferences, symposia and reports. There is a very full bibliography of 64 pages and an adequate index of 31 pages.

This is a full and comprehensive review of the cancer problem. As a publication it is first class—the format, the illustrations and the bibliography are excellent. The style of writing abounds in peculiarities of language or sentiment, for example, colloquialisms such as "because the cells have to get along with much less sex hormone than they are accustomed to" (p. 11), "to arrange a marathon between malignant and normal cells, with fairness to both" (p. 30), or "the kick given to susceptible cells" (by cosmic rays—p. 209), or remarks such as "there is of course a reason but it is obscure" (p. 223), or "viruses may be living agents and if so they are biological" (p. 228). Some of the early chapters are rather diffuse and perhaps somewhat too long, but the chapters on the chemical properties of cancerous tissues, on heredity, on modifying factors and on geographic frequency are particularly interesting. The book brings together competently in one volume a mass of information covering many fields of investigation. To do this in a subject which ranges so widely and to do it with up-to-date references is no mean achievement.

Histological Appearances of Tumours. By R. Winston Evans, T.D., B.Sc., M.R.C.S., L.R.C.P. (Pp. xvi + 773; illustrated. 90s. 0d.) Edinburgh and London: E. & S. Livingstone Ltd. 1956.

As with other crafts, skill in surgical histological diagnosis cannot be acquired without prolonged practical experience and in no other branch of clinical pathology is there greater need for close association with a master. Although monographs and atlases on pathological histology undoubtedly have their place and value, they can amplify but never satisfactorily replace such a personal training and the development of the visual memory that it inculcates.

The present volume provides a very full descriptive account of all the common, and many of the less common, human neoplasms with the noteworthy exception of those of the central nervous and female generative systems. As its title indicates, the letterpress is devoted primarily to those morphological considerations that aid the histologist in the identification of a tumour. With some of the more common ones, however, the discussions are more extensive, and attention is also directed to such additional matters as their clinical course, histogenesis, modes of dissemination and sites of metastasis. While much of the book is naturally based on the author's own experience and collection of material at the United Liverpool Hospitals, each section provides a comprehensive survey of current knowledge of some tumour and is supplemented by numerous references to relevant recent articles in British and American literature. It is a pity that more consideration has not been given to the copious Continental contributions in this field of Pathology.

Within its restricted scope, this monograph will serve a useful purpose and will undoubtedly prove helpful to many clinical pathologists called upon to undertake the diagnosis of tumours. The descriptions are clear and detailed, the index unusually full, and the illustrations, including nearly a thousand photomicrographs, for the most part of excellent quality and well reproduced in black and white half-tone blocks. The general production of the book is of a high standard, though it may be questioned whether the binding is sufficiently strong for a heavy volume in frequent demand for reference purposes.

Color Atlas of Oral Pathology. Prepared under the auspices of the U.S. Naval Dental School of the National Naval Medical Center, Bethesda, Maryland. (Pp. xiv + 188; illustrated. £5.) Philadelphia, Montreal: J. B. Lippincott Co. London: Pitman Medical Publishing Co. Ltd. 1956.

This is an excellent book and fulfils most adequately the objects set out in the preface, viz. "To present in concise form the fundamental facts concerning oral disease." It does not aim to be anything other than a book of pictures accompanied by the briefest of texts on the same page as and opposite to the illustration to which it refers. Considerable basic knowledge by the reader is taken for granted and because of this, though not suited for undergraduate students, it makes an excellent book of reference for the postgraduate and practitioner from which the salient facts—clinical, histological and, where necessary, radiological—can be easily ascertained on oral conditions, rare or common, likely to be encountered.

As is inevitable in a book of this type there are a few omissions. For example, the coverage of conditions found solely or mainly in children is extremely poor. Among such conditions of common occurrence—thrush, oral manifestations of the exanthematous fevers and the typical alveolar odontoclastoma (often called an osteoclastoma) which occurs during the period of resorption of the deciduous teeth are not mentioned nor are rarer conditions such as Ewing's tumour, cherubism, and the retinal anlage tumour of infants. Osteomyelitis of infants in the mandible or maxilla goes completely unmentioned and it is incredible that the completely erroneous statement that the cessation of mandibular growth following ankylosis due to infection or injury is caused by lack of functional stimulus should be made in this book.

The association of mandibular agenesis with first arch dysplasias is not pointed out and the inclusion of radiographs to show the difference in form in agenesis from this cause and in reduced or absent growth due to infective or traumatic injury to the condylar growth centre would be desirable. It seems a pity that while the histological picture of tuberculous lesions is well portrayed, that of syphilis is omitted.

The format, the paper and the standard of reproduction in colour is first class, in fact has to be seen to be believed, and it is obvious that in terms of value for money this book is a real bargain. The fact that with one exception criticism is of errors of omission demonstrates the high quality of the remainder of the book and there is no doubt that this volume makes a most valuable addition to the library of any practising oral surgeon or stomatologist to say nothing of the help it will give the postgraduate student. The U.S. Naval Dental School is to be sincerely congratulated upon its production.

Interesting Cases and Pathological Considerations and a Numismatic Suggestion. By F. Parkes Weber, M.A., M.D., F.R.C.P., F.S.A. (Pp. iv + 77; illustrated. 18s. 6d.) London: H. K. Lewis & Co. Ltd. 1956.

Books written by medical men well past the age of 90 are few and far between, and for that reason alone Dr. Parkes Weber's booklet will arouse considerable interest. But there are other reasons. Anything from the pen of this erudite and cultured physician, who describes himself as "a diligent student of pathological phenomena on the ways and byways of a long life of medical work", is worth reading. Of the twenty essays here assembled three are original ("Nævi and Nævoid Conditions", "Steiner Voerner Syndrome", and "A Numismatic Suggestion"). The others are reprinted in amplified form from such journals as *The Practitioner*, *British Medical Journal*, *Lancet*, *Medical Press*, and *British Journal of Children's Diseases*. In the first article "My Most Interesting Case", printed in the full form in which it was submitted to *The Practitioner*, the author reminds us that he described thrombo-angiitis obliterans just before Leo Buerger's first publication. The papers vary in length from half a page to fourteen pages. The majority are dated 1954 and 1955. The earliest "A Portrait Medal of Paracelsus" first appeared in 1897. Some of the titles in their length and completeness are typical of the writer, as are the copious footnotes, references, and parentheses. There is a good index.

New Pathways in Cellular Pathology. By Gordon Roy Cameron, M.B., D.Sc.Melb., F.R.C.P., F.R.S. (Pp. vii + 90; illustrated; 16s. 0d.) London: Edward Arnold. 1956.

The introduction of various biophysical techniques into cytology in recent years has made it possible to penetrate far into the obscurities of many intracellular phenomena. Hitherto, these methods, among them the centrifugal separation and electronmicroscopic examination of distinctive organelles, such as the nucleus, mitochondria and microsomes, have been

employed mainly in seeking a better understanding of the localization of particular structures and functions in normal cells. In this small monograph, the amplification of two recent lectures, Professor Cameron has pointed out the great and productive field of research that awaits the pathologist when he turns his attention to the study of injured cells by similar methods. Naturally, in a rapidly expanding science in which many of the findings obtained by these new methods have not yet been fully fused with those of conventional microscopy, much must for the present be speculative. But enough has already been added to established knowledge for it to be no longer possible for the pathologist to remain aloof. Professor Cameron has performed a valuable service in bringing a broad survey of this modern cytology to the notice of a group of medical scientists, many of whom are conservative by nature and training. None the less, it may well provide an incentive to some of the younger and more enterprising to examine more fully for themselves the great possibilities inherent in the newer cytology.

Progress in Nuclear Energy. Series VII Medical Sciences. Vol. 1. Editors J. C. Bugher, J. Coursaget, and J. F. Loutit. (Pp. xii + 165. 42s.) London: Pergamon Press Ltd. 1956.

There are seven different contributions to this Series of Progress in Nuclear Energy. Two deal with the growing use of radioisotopes in medical diagnosis, two with advances in technique in radiotherapy by internal or external means with the aid of nuclear radiations, two with the present-day principles and standards of radiation safety and one is devoted to dosimetry of ionizing radiation. The source of these articles is mainly attributable to the International Conference on the Peaceful Uses of Atomic Energy at Geneva, August 1955. Although two of the articles here are devoted to the diagnostic value of radioisotopes, one is by two physicists and the other by a medical man. There is in no sense an overlap, however, and a very wide range of use is exhaustively treated; in fact, the first of them concludes with a bibliography extending over seven pages.

The two articles on therapy are by a master hand and in his Introduction he expresses the view that the therapeutic use of radioactive isotopes administered internally is of more fundamental interest than their use as external sources. Then follow contributions by other authors about this particular technique, upon hæmatologic therapy and the treatment of neoplasia generally either by radioactive suspensions or by colloid chromic radiophosphate, and an "accurate method" for the treatment of hyperthyroidism with I^{131}. The writer concludes that this substance is his choice in the treatment of Graves' disease in patients over 40 years of age and for younger patients with post-therapeutic recurrences.

Within this group of papers upon treatment is one dealing with various problems in the whole range of effort involving the internal use of radioisotopes. One of the biggest problems lies in the estimation of the doses received by various tissues; at present "it is rarely possible to make more than a crudely approximate evaluation of the mean tissue dose, at the best $\pm 20\%$ and often with much greater error". An important unsolved problem is whether there is any real risk of late carcinogenesis or of leukæmogenesis; time alone can give the answer, but to date the absence of any proved cases is reassuring. There are other dangers, however; the intravenous administration of 6 millicuries of P^{32} delivers a dose in the region of 100 rep to the testis or ovary.

In spite of these possibilities, the reader gets the general impression that the hazards can be met with equanimity, largely because of the general awareness of the dangers that are there when radioisotopes enter the body.

This volume of 165 pages is a mine of information which will be of the greatest service to those already, and to those about to become, engaged in a rapidly developing branch of medicine.

Noradrenaline—Chemistry, Physiology, Pharmacology and Clinical Aspects. By U. S. von Euler, M.D., F.A.C.P.(Hon.) (Pp. xxi + 382; illustrated. 87s. 6d.) Oxford: Blackwell Scientific Publications. (Springfield, Ill.: Charles C. Thomas.) 1956.

The appearance of a monograph on noradrenaline is to be welcomed especially from the hand of one of the most vigorous workers in this field. The book covers in considerable detail the vicissitudes of noradrenaline since its synthesis in 1904 by Stolz to its present position as one of the transmitter substances involved in nervous activity. Once identified as being present in the organism in 1946–8 by von Euler and his co-workers, noradrenaline has become the subject of a very voluminous and scattered literature. Sir Henry Dale in a characteristic introduction surveys the history of noradrenaline. He had studied its general pharmacological action along with Barger in 1910–11, and had noted that this primary amino homologue of adrenaline reproduced the inhibitor components of the

action of adrenaline relatively weakly, making it more accurately sympathomimetic in its detailed action than adrenaline. Somewhat ruefully with all the newer evidence now available he remarks that this fact made it more difficult for him to accept T. R. Elliott's hypothesis of adrenaline having a chemical transmitter function in sympathetic nervous stimulation. Later evidence has, however, clarified the situation—the transmitter being composed of mainly noradrenaline and adrenaline, noradrenaline being the more predominant constituent at many nerve ends. This evidence relieves us of the necessity of preserving Cannon's sympathin with its E. and I. modifications. It is suggested that the sympathin nomenclature should now be dropped as being misleading and unnecessary—the terms have served their purpose.

After a brief historical introduction the chemistry and metabolism of noradrenaline, methods of purification and biological assay are discussed in great detail, and its occurrence in the suprarenal medulla, chromaffin cells, and in nervous organs and body fluids is carefully studied. The physiology and pharmacology are dealt with in great but necessary detail followed by a description of the part it plays in adrenergic nerve stimulation and also in suprarenal and other chromaffin gland secretion and its excretion in the urine. The more recent discovery of noradrenaline in chromaffin cell tumours and sympathoblastomata and its significance are also discussed. The final chapter is devoted to a survey of the therapeutic uses of noradrenaline. This brief survey of its main contents shows that the book has a wide appeal not only to pharmacologists but to biochemists, pathologists and clinicians; in fact to all with an interest in this rapidly growing field of investigation—growing so rapidly that most of the chapters have a short series of addenda of the even more recent papers. The format and presentation are those customary for this series. The book is profusely supplied with tables and figures. While the price of the book may prevent some individual workers from having their own copy, it will be essential for all laboratories where such problems are studied.

Clues in the Diagnosis and Treatment of Heart Disease. By Paul D. White, M.D. 2nd edit. (Pp. xv + 190; illustrated. 40s.) Oxford: Blackwell Scientific Publications. (Springfield, Ill.: Thomas.) 1956.

The first volume of this small book was written at the request of medical graduates who had found a lecture on the subject by the author to be pregnant with interest and instruction. The demand for a second edition within so short a time has endorsed its usefulness. Elaborate and specialized laboratory procedures in the diagnosis of heart disease take second place here to the important knowledge that is so readily accessible to the clinician when he elicits the story of an illness from a patient and uses intelligently the natural senses during examination conducted in the patient's home or in the hospital ward. This book is intended for general practitioners, but cardiologists cannot be unmindful of the succinct statements that appear on almost every page, and the quotation—"a doctor who cannot take a good history and a patient who cannot give one, are in danger of giving and receiving bad treatment", might be mentioned as a sample. The clues it embodies are not all of the author's discovery, and they gain in value from being representative of opinion held by clinicians all over the world. Paul White can listen to, and learn from, others, and thereby add to his own bountiful store of knowledge and wisdom which he imparts delightfully to the readers of this valuable little book.

Alcoholism. A Manual for Students and Practitioners. By Lincoln Williams, M.R.C.S., L.R.C.P. (Pp. x + 62; 8s. 6d.) Edinburgh and London: E. & S. Livingstone Ltd. 1956.

Medical students receive little instruction in alcoholism from their teachers or from their textbooks, with the result that when they begin general practice, the question of alcoholism is a real problem to them. Dr. Lincoln Williams describes his little book as "a manual for students and practitioners". Convenient in size, simply and sympathetically written, and commendably inexpensive, it is needed by, and it will appeal to, both types of reader. The author rightly looks upon alcoholism not as moral depravity, but as a disease and, therefore, as a medical problem, and throughout he stresses the fact that it is also an individual problem. In fourteen short chapters, some of which are only a page or two in length, he discusses drinking patterns; personality factors; the course of alcoholism; heredity; the mental and physical effects of alcoholism; how to approach an alcoholic; medico-legal aspects of alcoholism; methods of detoxication; disruption of the drinking pattern (by conditioned-reflex treatment, apomorphine, and Antabuse); group therapy; and Alcoholics Anonymous. The book concludes with a useful bibliography and an index.

Section of Pathology

President—Professor JOHN W. S. BLACKLOCK, M.D.

[*October* 16, 1956]

Injury as An Ætiological Factor in Tuberculosis

PRESIDENT'S ADDRESS

By Professor JOHN W. S. BLACKLOCK, M.D.

FROM time to time clinicians have drawn attention to the liability of tuberculosis developing after an injury at such sites as the bones, joints, epididymis, chest wall (pleurisy) and head (meningitis) and have stressed the fact that the trauma was usually of a trivial nature (Keen, 1906; Watson-Cheyne, 1911; Hamburger, 1912; Borthwick, 1945). Krause (1899), who repeated the classical yet controversial experiments of Schüller (1880), showed in rabbits and in guinea-pigs infected with tuberculosis that the disease rarely if ever occurred at the site of fracture but was frequent in joints which had been wrenched. More recently Debré *et al.* (1951*a*) have again drawn attention in a case, which was well investigated, to the effect of trauma localizing a tuberculous infection at the seat of injury.

The same is true of syphilis, gummata occurring at the site of trivial injury, for example on the forehead due to touching the ground many times daily during devotional practices (Lacapère and Laurent, 1918), or in scars (Chesney *et al.*, 1928), or in tattooed ar as (Aoki, 1912; Keidel and Zimmermann, 1918) though in such cases the areas tattooed with pigments containing mercury (e.g. cinnabar) remained free from lesions. As in tuberculosis, these observations have been confirmed by experimental work on the part of some of the above authors. Secondary lesions have been reported at the site of injury in many other infections—typhoid, the pyogenic group, and also those due to the viruses, as was reported as long ago as 1804 by Jenner in the case of vaccinia.

The explanation usually given is that the injury produces a "locus minoris resistentiæ"—a venerable expression, hoary with age, which means but little.

My interest in this problem, as far as it concerns tuberculosis, was stimulated by the publication of a case by Ebril and Elek (1946) in which tuberculosis occurred at the site of a penicillin injection. They stated: "The source of the infection was in all probability either the penicillin or the apparatus for its administration." Others have reported similar cases (Hounslow, 1946; Coope and Hindenach, 1947; Forbes and Strange, 1949; Douglas, 1950; and Šikl and Vaněk, 1950), and opinion varies among those authors as to whether the infection was autogenous or exogenous. The case described, however, by Coope and Hindenach in which tuberculous abscesses developed in both thighs at the site of injections suggests a hæmatogenous origin. The tubercle bacillus had been typed and proved to be human in only one of the reported cases (Forbes and Strange). Debré *et al.* (1951*b*) have reviewed the literature of syringe-borne tuberculosis, to which attention was first drawn by Bigger *et al.* (1940*a*). During 1947 to 1948 I was asked to investigate three cases of tuberculous abscesses occurring at the site of penicillin injections. The salient features of these cases are as follows:

Case I.—Male, aged 20. Active pulmonary tuberculosis with positive sputum (human type of bacillus). Treated for boils with penicillin injections into the outer aspect of thighs. About four weeks after cessation of treatment an abscess developed in each thigh in the region of the injections, from which human type of tubercle bacilli were isolated in pure culture.

Case II.—Boy, aged 14. Cervical abscess with enlarged glands. Clinically this was thought to be pyogenic and penicillin injections were given. In tissue taken from the lesion pyogenic cocci as well as human type of tubercle bacilli were isolated; histologically typical tubercle follicles were present. The penicillin injections had been given into the buttock, and about six weeks after the cessation of treatment an abscess developed in that region from which human type of tubercle bacilli were isolated in pure culture.

Case III.—Female, aged 28. Treated for a pyogenic infection of a wound by penicillin injections into the outer aspect of thighs. An abscess developed in both thighs about eight weeks after the last injection; human type of tubercle bacilli were isolated from each abscess. After the thigh-abscesses were proved to be tuberculous, radiological examination showed a healing lesion in the upper lobe of the left lung, but no tubercle bacilli were ever obtained from the scanty sputum.

These cases, particularly Cases I and III, in which tuberculous abscesses were present in each thigh, suggested to me that the infection at the site of the penicillin injection was almost certainly hæmatogenous. The first two cases occurred in hospitals where the syringes were reserved exclusively for injections and were boiled for at least ten minutes before being used. The third case occurred in the domiciliary practice of a practitioner who used

only one particular syringe for injection, washing out the syringe and needle several times after use with surgical spirit, a procedure which, as pointed out by Bigger *et al.* (1940), is not sufficient to kill tubercle bacilli.

Tuberculous lesions in muscles are a rarity and the literature, chiefly Italian, has been reviewed by Cortessi and Venturi (1948), who collected 92 cases and added 2 of their own. Some of their cases, apart from those due to trauma may, however, have been of the nature of syringe-borne tuberculosis, as the tuberculous lesions at the site of injection followed auto-therapy, anti-typhoid vaccination, &c. The authors concluded, however, that all the infections were hæmatogenous, owing to the presence in a proportion of the cases of tuberculous lesions elsewhere (lungs, glands and bones).

The possibility suggested itself to me of finding if experimental tuberculosis could be localized at the site of various types of injury, in particular those due to injections of penicillin and other substances as the trauma due to this procedure was minimal. A series of experiments was accordingly carried out, only brief details of which will be given here as they are being published in full elsewhere by my colleague, Dr. J. R. B. Williams, and myself.

Conditions Necessary for Experiment

An experimental approach to this subject demanded (1) a tuberculous bacillæmia, (2) trauma of various kinds of which that of a minimal degree would give the least controversial results, owing to the avoidance, as far as possible, of injury to the blood vessels causing hæmorrhage and allowing the bacilli to escape into the damaged tissues. For the first we found that injection of approximately 500,000 human tubercle bacilli (H.37Rv) in 0·5 ml. saline into the left ventricle of rabbits was the most satisfactory procedure. To accomplish this, the thorax was opened in order that the manipulation could be undertaken visually as this ensured that the bacilli had actually entered the arterial side of the circulation. Similar experiments were performed on guinea-pigs but in these the dose of bacilli was approximately 125,000 bacilli in 0·25 ml. saline. By this means it was found that in rabbits tubercle bacilli could be isolated from 1 ml. of blood from fifteen minutes to twenty-four hours after inoculation. Of much importance, as it helps to explain the mechanism of infection of an injured site, was the finding that in rabbits tubercle bacilli could be isolated from catheter specimens of urine within two hours of inoculation, and at varying intervals up to twenty-four hours. At this early time it is not possible for any gross lesion to have developed in the kidney and the only explanation likely is that the tubercle bacilli had passed through the glomerular capillaries into the sub-capsular space and so into the urine.

For the production of trauma, various forms of injury were used, the chief being the injection into the muscles of penicillin, saline, peptone or other substances, as mentioned later, the site of such injections being marked on the overlying skin, though this was not altogether a trustworthy guide.

It was assumed that any tuberculous lesion developing in the muscles at the site of injury was due to the injection, as muscle tuberculosis in the animal experimentally infected with small doses of human strains, is, as in man, exceptionally rare. Such small doses (500,000 bacilli) as were employed in rabbits produced a very chronic disease, the animals, when allowed to live, being still apparently healthy six months later. This rarity of muscle tuberculosis in the rabbit experimentally infected with small doses of tubercle bacilli has also been commented on by Cobbett (1917); Calmette (1928) in his monumental work on tuberculosis makes no mention of muscle lesions, and neither do Corper and Lurie (1926) in their work on the localisation of tubercle bacilli in the tissues of different animals. Indeed, in our own experiments muscle tuberculosis was never found until after the sixth week of infection and then only with extreme rarity, though many blocks of muscle tissue were examined. The lesions occurring after the sixth week of infection may, of course, have been due to a secondary spread from lesions in the various viscera caused by the original inoculation. In the case of guinea-pigs, muscular lesions were never observed. The rarity of muscle lesions may be due to lactic acid, which is produced in muscles, having an anti-mycobacterial effect (Dubos, 1953).

The Effect of Trauma to Muscles

As was to be expected, the coarser forms of trauma such as the removal of a piece of muscle, severe blows, the insertion of ligatures, almost invariably resulted in a tuberculous lesion developing at the site, due possibly to the bacilli escaping from the severed vessels into the damaged tissues. The fact that experimental pyogenic infections sometimes localized around stitches was observed nearly a century ago by Billroth (1865). Silk ligatures which we used contain a relatively high proportion of silicate. Kettle (1924) showed experimentally in mice and in rabbits infected by the intravenous route with tubercle bacilli (human or bovine) that silica introduced into the muscles caused a heavier concentration of tubercle bacilli at that site than did turpentine or calcium chloride, both of which

caused a more acute inflammatory response. Indeed, Kettle's Presidential Address to this Section in 1931 dealt partly with this very subject.

The more minimal forms of injury such as intramuscular injection were studied in three groups of rabbits, all infected by the intracardiac route as already described. On the day of infection and the day following the animals in group (*a*), 10 rabbits, were injected with 0·3 ml. saline intramuscularly; in group (*b*), 10 rabbits, were injected with 0·3 ml. crystalline penicillin (300,000 units per ml.); and in group (*c*), 4 rabbits, were injected with 0·3 ml. 2% peptone. The animals were all killed before the sixth week of infection and the muscles at the sites of the injection were investigated histologically for tuberculous lesions as well as uninjected muscles at some distance from those sites to serve as controls. Tuberculous lesions were found: in group (*a*), saline—in 2 out of 10 injected on the first day of infection and in none on the second; in group (*b*), penicillin—in 6 out of 10 on the first day and in 4 out of 10 on the second; in group (*c*), peptone—in all 4, both on the first and seconds days (Figs. 1 and 2). In all these groups no tuberculous lesion was found in the

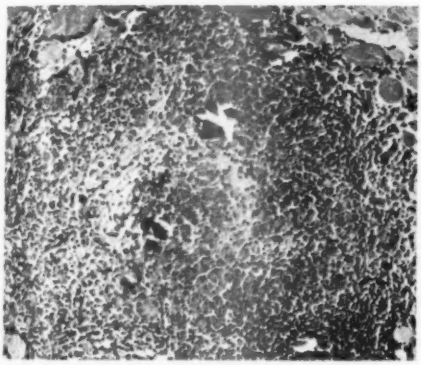


FIG. 1.—Tuberculous lesion at site of intramuscular injection of penicillin. Caseous centre and surrounding cellular reaction. × 90.

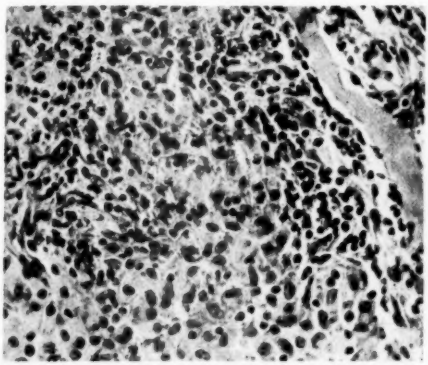


FIG. 2.—Tuberculous lesion at site of intramuscular injection of peptone. Endothelioid cells with some large mononuclears and round cells. × 230.

control muscles. It is unfortunately not desirable to apply any test for statistical significance to these results on account of (1) the difficulty of always finding the site of injection and (2) the variation of the response to tuberculous infection on the part of a mixed strain of rabbits, as commented on by Lurie (1928). It is apparent, however, that the tuberculous infection localized much more frequently at the site of injections of penicillin and of peptone, given on the first or second day of infection, than at the site of injections of saline. This finding, together with the absence of lesions in muscles not injected, is of some significance. Undoubtedly, as we shall afterwards point out, the penicillin and peptone had introduced another factor.

These experiments were repeated in guinea-pigs which had been infected by the same route as the rabbits, but with 0·25 ml. of a suspension containing approximately 125,000 bacilli of the same strain. In guinea-pigs, however, distaquaine penicillin required to be used in place of crystalline owing to these animals quickly wasting and dying in a few days after the injection of the latter. 0·2 ml. of distaquaine penicillin (300,000 units per ml.) was found to be fairly well tolerated, probably owing to the slower absorption of the penicillin.

The experiment was carried out on similar lines to that in the rabbits, injections being made into the muscles on the day of infection and on the day after in (*a*) 14 pigs—0·2 ml. saline; (*b*) 16 pigs—0·2 ml. distaquaine penicillin; (*c*) 6 pigs—0·2 ml. of the agent used for suspending the penicillin; (*d*) 4 pigs—0·2 ml. of 2% peptone. When these animals were killed twenty-eight days or less after the last injection, tuberculous lesions were found in the muscles at the injection site in group (*a*) saline—in none out of 14 injected on the first day and in 4 out of 14 on the second; in group (*b*) penicillin—in 4 of 16 on first day and 7 of 16 on second; in group (*c*) suspending agent—in 4 of 6 on first and second days; in group (*d*) peptone—in all 4 on both first and second days.

Though the results, on account of the same difficulty as experienced with rabbits, cannot be submitted to statistical proof, they are indicative that the penicillin, the suspending agent and the peptone are more liable to localize a tuberculous infection at the site of injection than saline. In all these groups, sections taken from the muscles not injected in each animal showed no tuberculous lesion.

The Effect of Trauma to Joints

It is recognized, as already mentioned, that injury to a joint in the human subject with primary tuberculosis elsewhere occasionally results in tuberculous disease of the joint. We decided to try if we could prove this experimentally. Tuberculosis of the joints of rabbits experimentally infected with human type of tubercle bacilli may occasionally occur even when the disease is pursuing a chronic course. This has been noted by Cobbett (1917) and also by Calmette (1928). In a series of 12 rabbits killed up to forty days after infection with the dose of bacilli used in these experiments, we never observed any histological evidence of tuberculosis in the larger joints like the knee or the elbow. In another 6 rabbits, 0·1 ml. of crystalline penicillin (500,000 units per ml.) was injected into the right knee and right elbow about one hour after intra-cardiac infection. In 4 the knee and in 6 the elbow showed histological tuberculous lesions in which tubercle bacilli were demonstrable when the animals were killed forty days or less after the infection (Fig. 3). The corresponding joints on the opposite side of these animals showed no lesions histologically. In another series of rabbits in which joints were struck a sharp blow, tuberculous lesions were observed in a high proportion of the injured joints, but in these it was obvious at the time of experiment that some bruising of the superficial tissues had occasionally resulted.

Primary Lung Focus Experiments

The tuberculous bacillæmia produced by intra-cardiac inoculation is highly artificial and bears little resemblance to what may happen in the human subject with, say, a tuberculous lesion in the lung, though sometimes in these cases tubercle bacilli do find their way into the blood stream to produce secondary lesions in kidneys, bones, joints, meninges and elsewhere. It was decided, therefore, to make an attempt to produce a lesion in the lung of the rabbit and of the guinea-pig, resembling the primary lung focus in the child, as described by Blacklock (1932). Insufflation of tubercle bacilli into the trachea caused multiple lesions in the lungs and, therefore, was undesirable. It was found that by injecting 0·02 ml. of a suspension containing approximately 500 bacilli into the superficial part of the lung, exposed at thoracotomy, a lesion closely resembling the primary lung focus of the child could be produced. Indeed, in the successful experiment the resemblance was striking for, as in the child, the infection also spread by the peribronchial lymphatics to the hilar glands and thereafter became generalized.

In a small series of rabbits in which these lung foci had been produced, it was noted that the spread of the disease to the other lung and the other organs did not become histologically apparent until about the fourth week and it was assumed that shortly before this time tubercle bacilli were escaping from the lung lesion into the blood stream. To test this assumption coarse silk threads were inserted into the muscles of 2 rabbits during the first, second, third and fourth weeks, after the injection of tubercle bacilli into the lung, as already described. Tuberculous lesions occurred only around those ligatures inserted during the fourth week.

In a further series of 11 rabbits infected in the same way to produce a primary lung lesion, intramuscular injections of 0·25 ml. of crystalline penicillin (300,000 units per ml.) were made during the fourth and fifth weeks of infection. Of the 11 injections made during the fourth week, 2 showed evidence of tuberculous infection at the site of the injection in the muscle, as also did 3 of the 11 injections made during the fifth week (Figs. 4 and 5). In all these animals lung foci had been produced, and in addition there was histological evidence of tuberculous involvement of the other lung and occasionally of the spleen and kidneys. Similar experiments were carried out in guinea-pigs, using distaquaine penicillin for intramuscular injection, but in only 1 out of 4 did a lesion result at the site of the intramuscular injection, though all showed, in addition to the lung focus, generalized involvement of the other organs.

Though disappointing, these results do resemble what occurs in the human subject with pulmonary tuberculosis, as in the human the occurrence of secondary tuberculous lesions at the site of injury is not common.

The possibility then suggested itself, could a tuberculous infection be localized in the lung after a primary infection of the thigh muscles? It is well recognized that in the rabbit the lung is one of the organs most affected, irrespective of the route of infection. Indeed Dr E. G. Rees and I have found that human tubercle bacilli injected into the suprarenal localize very quickly in the lung. A small series of experiments, as yet incomplete, are in progress in which human tubercle bacilli were inoculated into the muscles of the right thigh and seven to fourteen days later 0·1 ml. of indian ink (to serve as a guide) was injected superficially into one aspect of a lobe of a lung and into the corresponding site on the other aspect 0·1 ml. of crystalline penicillin (500,000 units per ml.). In some of the animals killed about two months later the infection was found to have localized at the site of these injections, producing at the penicillin site an appearance very similar to that seen where

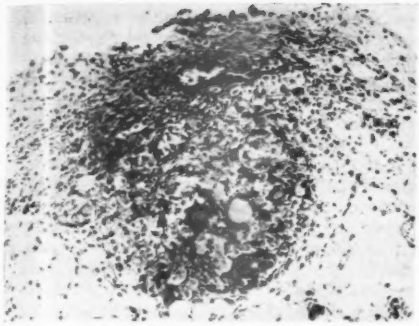


FIG. 3.—Tuberculous lesion in knee-joint injected with penicillin. Tubercle follicle with giant cell in fatty tissue below synovial membrane. × 100.



FIG. 4.—Lung focus produced by direct inoculation of tubercle bacilli into lung of rabbit. × 10.

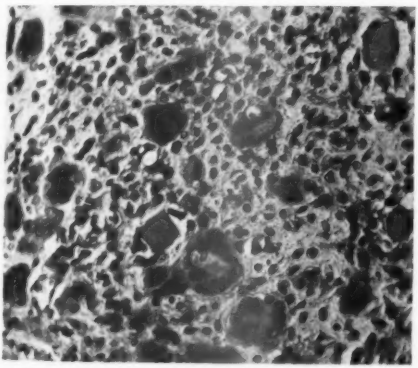


FIG. 5.—Same rabbit as Fig. 4. Tuberculous lesion in thigh muscles injected with penicillin five weeks after tubercle bacilli had been inoculated into lung. Endothelioid and giant cells: small fragment of muscle tissue. × 200.

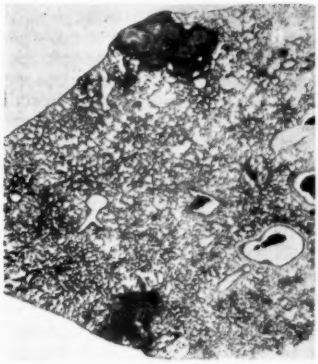


FIG. 6.—Tuberculous focus in lung of rabbit at site of penicillin injection (top): lower focus due to injection of indian ink to serve as marker for site of penicillin injection. Rabbit had been infected by inoculation of tubercle bacilli into thigh muscles seven days before injections of penicillin and ink into lung. × 5.

the bacilli had been injected directly into the lung to produce a primary lung focus (Fig. 6). Such a result may serve to explain why tuberculosis of the lung so frequently follows such diseases as measles, whooping cough and influenza, in which we know the lungs are injured by the inflammatory processes occurring in these diseases.

THE FACTORS INVOLVED IN THE LOCALIZATION OF THE INFECTION

In these experiments there was a tuberculous bacillæmia, and any gross injury, such as bruising, would allow the bacilli to escape from the ruptured capillaries, or, if short of rupture the capillaries were so damaged as to cause thrombosis, then the bacilli might become arrested at the site of the thrombosis and there multiply, a tubercle follicle eventually forming around them. This is the likely explanation of some of the experiments in which a tuberculous lesion resulted at the site of a blow or in the area where silk or wire sutures had been introduced. But it is hardly sufficient to explain the positive results at the sites of injection of penicillin or peptone as in these hæmorrhage was a rarity and the small needle used (size 18) would not be likely to cause sufficient trauma to produce thrombosis.

The other factor was the effect of the penicillin or the peptone on the tissues into which these substances had been introduced. With the early penicillin preparations, most of which were not absolutely pure, local reactions at the site of injection, such as necrosis,

œdema, and cellular infiltration, sometimes occurred (Robinson, 1943; Selbie and McIntosh, 1943; Hamre *et al.*, 1943; Darmady, 1946). But this has not been reported with the purer crystalline forms. To ascertain if any damage resulted, 0·2 ml. crystalline penicillin G (20,000 units) was injected into the muscles of a series of guinea-pigs, marking the site of injection in the overlying skin. In a few of these animals killed on the fourth day a small microscopic necrotic focus with surrounding macrophage reaction was found. These foci were also observed in some of the animals as late as the seventh day after injection, but not afterwards. It was not easy to find such lesions and the muscle at the site of injection required to be serially sectioned. Of interest to us, however, was the macrophage response in these areas. Peptone injections produced a greater reaction on the part of these cells than did penicillin. The macrophages were probably attracted to the site by the foreign substances injected and in those experiments where the animals had been previously infected with tuberculosis, some of these cells, having already phagocytosed tubercle bacilli in the perivascular regions of the capillaries, might have carried them to the site of injection. It is well known that the large mononuclear leucocyte actively phagocytoses tubercle bacilli (Sabin and Doan, 1927; Lucké *et al.*, 1933; Lurie, 1932, 1934; Vorwald, 1932; Jensen *et al.*, 1935), and in the cytoplasm of these cells the bacilli may multiply and survive for at least a time (White, 1927; Lurie, 1942; Suter, 1952), though as the bacilli multiply, particularly the H.37Rv strain as used in these experiments, the mononuclears die. The death of these infected cells has been reported to be more rapid in the presence of penicillin by Mackaness (1952), though penicillin has been extensively employed as a bacteriostatic agent in tissue culture (Gey *et al.*, 1945).

To help to explain what was occurring a small series of guinea-pigs were injected *intraperitoneally* with (*a*) 2 ml. crystalline penicillin (60,000 units), or (*b*) 2 ml. peptone (2%), or (*c*) 2 ml. saline; the animals were killed one to two days later. In films made from the scanty fluid in the peritoneal cavity, the cellular response in groups (*a*) and (*b*) killed one day after intraperitoneal injection consisted of polymorphs, lymphocytes and mononuclears, while in those killed two days afterwards the cells were mainly mononuclears. In group (*c*) very scanty cells were found. On histological examination of the omentum from these animals, an increase in mononuclear cells was observed, particularly around the capillaries and it seemed possible that it was these cells that were conveying the bacilli from the region of the capillaries into the peritoneal cavity. To verify this assumption, 26 guinea-pigs were infected by the injection of tubercle bacilli (H.37Rv) introduced into the left ventricle, as previously described. On the day of infection or the day after, the peritoneum was injected with (*a*) 2 ml. peptone solution—4 pigs; (*b*) 0·5 ml. crystalline penicillin (60,000 units)—14 pigs; (*c*) 2 ml. saline—8 pigs. In films made from the peritoneal exudate of group (*a*) scanty tubercle bacilli were found in all 4 animals, and in group (*b*) in 10 of the 14, whereas in group (*c*) no bacilli were found in any of the animals. The bacilli were chiefly found inside large mononuclear cells (Fig. 7) and cultures of the



FIG. 7.—Macrophage (from peritoneal fluid of guinea-pig) containing several tubercle bacilli; peritoneum injected with penicillin on day of intracardiac infection with tubercle bacilli. × 650.

scanty peritoneal exudate in such cases yielded a few colonies of tubercle bacilli on Löwenstein's media, whereas in all the other cases no growth was obtained. It thus seemed a reasonable conclusion that the large mononuclear leucocyte was the vehicle by which the bacilli were conveyed from the region of the vascular system to the site of injury. It is known that the capillary vessels of the mesentery and omentum are more permeable to suspended particles than the capillaries elsewhere (Cappell, 1930). Kusnetzowsky (1929) has also shown that in inflamed areas particles of indian ink pass through the endothelial cells and are phagocytosed in the extra-vascular spaces by polyblasts; Menkin and Menkin

(1931) have also demonstrated the same for graphite particles. The cellular reaction around sites of minor trauma, including those due to intramuscular injections, is mainly on the part of the mononuclear cells, whereas with more severe injury involving the death of more tissue, more polymorphonuclear leucocytes are attracted in the first place.

Another factor which should be considered is the possible liberation of histamine from the focus of injury and the part played by it. Findlay (1928) was able to localize hæmatogenous pyogenic infections as well as vaccinia at the sites of intramuscular injections of histamine. It would be interesting to repeat his experiments in a tuberculous infection. Histamine undoubtedly will be liberated in areas of more severe injury and will cause some increased permeability of the capillaries of the part, but it is doubtful if sufficient is liberated as the result of a simple intramuscular injection, which admittedly may cause temporary interstitial pressure changes, which might have some transient effect on capillary permeability. Sager and Nickel (1929) have also demonstrated how *Streptococcus viridans* introduced intravenously will localize at the site of sterile abscesses produced by 10% silver nitrate solution, and Kettle (1924) showed how tubercle bacilli inoculated intravenously localize at the site of silica injections.

The very controversial question now arises, where do these mononuclear leucocytes arise? Advisedly we have used this term for these cells as it makes no definite implication as to their origin. Sabin *et al.* (1925), Sabin and Doan (1927) and Cunningham *et al.* (1925) maintain that the mononuclear cells are derived from the clasmatocytes and are of reticuloendothelial origin, and that they actively phagocytose tubercle bacilli, whereas the monocyte, which appears later, is not so phagocytic and eventually differentiates into the epithelioid cell. They observed that the monocytes in the peripheral blood in acute experimental tuberculosis may harbour but probably do not destroy tubercle bacilli. Cappell (1930) from his extensive experiments on vital staining concluded that only a small proportion of the mononuclear cells of the tissues is derived from the monocytes of the blood or from the tissue histiocytes, and that their main origin is from the cells of the adventitial sheaths. Ebert and Florey (1939) found that at least some of the mononuclear leucocytes originate from the blood monocyte and that the tissue histiocyte does not migrate into an injured area but that mononuclear phagocytes may develop in the tissues. From our own observations in experimental tuberculosis we have been impressed that in the very early stages of an infection large numbers of mononuclear leucocytes (macrophages) are found around some of the smaller blood vessels in the infected region, and most likely the majority of these cells originate in that situation from some stem cell. Lurie (1934) has made similar observations and has further noted that these collections of mononuclear cells push the endothelial lining of the vessel ahead of them and so encroach on the lumen, thus being in a most advantageous position for phagocytosis of any bacilli in the blood stream which may become slowed at this point, due to the narrowing of the capillary.

Lastly the effect of the penicillin and the peptone on the localization of the infection must receive some consideration. It was observed during the progress of this work that where saline was injected bacilli rarely, if ever, localized; in the few cases where this happened a small vessel may have been pierced by the needle, allowing blood and bacilli to escape. Ungar and Muggleton (1946) have reported that the addition of penicillin to culture media resulted in an increased growth of the tubercle bacillus, while Iland and Baines (1949) from their experiments concluded that on account of the penicillinase produced by this organism it had no such effect, though their experiments were not identical with those of the former workers. Rivière *et al.* (1947) found that guinea-pigs infected with tubercle bacilli and treated with penicillin die much more rapidly than the controls not so treated. On account of the extreme toxicity of penicillin for these animals it seems more likely that death was accelerated by the penicillin alone. To find if penicillin had any effect on the progress of tuberculous infection in rabbits we infected 4 rabbits by intravenous inoculation with 0·01 mg. tubercle bacilli (H.37Rv) and another 4 with the same dose into the left ventricle. To 2 of the intravenous group and 2 of the left ventricle group, 1 ml. of crystalline penicillin (100,000 units) was injected intravenously every day for four weeks. The other 4 were given no injections and served as controls. All 8 animals were killed four weeks after the penicillin group had received their last injection, when no difference was found in the severity or the distribution of the lesions in those which had received penicillin and those which had not. Thus we can conclude that at least in the rabbit penicillin does not stimulate the growth of tubercle bacilli as judged by the lesions produced.

When all the results of these experiments are considered the conclusion, though still controversial, may be reached that the macrophage is responsible for carrying the infection. Thus a cell which does so much for the surgeon, scavenging dead tissue and phagocytosing ligatures, and for the physician by removing the products of deep-seated inflammation in the lung and elsewhere has been found wanting. For having phagocytosed the tubercle bacilli in the blood stream, but more probably in the immediate vicinity of the capillaries, it

still goes on carrying out its normal function by being attracted to a foreign substance introduced into the tissues or by damaged tissue and thus spreads the disease.

It is my privilege to thank my two colleagues, Dr. J. R. B. Williams and Dr. E. G. Rees, who have helped me in some aspects of this work, and for their permission to use some of our joint work, as yet unpublished, for this Address. I would also wish to express my gratitude to two technical assistants, Miss June D. Hart and Mr. Geoffrey Brown, who at different times have given me invaluable assistance, and also for secretarial assistance to Miss M. Ash.

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Section of Physical Medicine

President—A. C. BOYLE, M.D., M.R.C.P.

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Joint Contractures in Children

By DENIS BROWNE, F.R.C.S.

JOINT contractures in children may be classified into the congenital and acquired, and these classes divided again according to whether the contracture is intrinsic or extrinsic. In the intrinsic class the limitation of movement is due to structures of the joint itself, particularly the fibrous tissues round it; in the extrinsic contractures the limiting structures are outside the joint, most usually being muscles, though occasionally webbing of the skin is responsible.

CONGENITAL CONTRACTURES

Intrinsic

(1) *Normal contractures:* It is not often pointed out that normal newborn babies have the limitations of the adult range of joint movement which might be expected from their previous cramped position. The hips, the knees, and the elbows will not fully extend; and the feet will not go into full equinus. The normal instinctive muscular movements of this age soon dispose of these slight limitations.

(2) *Contractures due to abnormal pressure:* In my opinion long-continued pressure on a limb has the same effects if it occurs before birth as it is generally recognized to have if it occurs afterwards. These effects seem to be due to an interference with the normal blood circulation, particularly the venous return, which of course would become obstructed at a much lower pressure than the arterial. This increased pressure may be either mechanical, due to the uterine structures not expanding at the correct rate to keep pace with the expansion of the growing fœtus; or hydraulic, due to increased tension of the amniotic fluid. Though increased tension of this fluid is usually associated with increase in its amount (that is to say hydramnios) increased tension may be present without increased amount, and increased amount without increased tension. The classical example of this process is the degeneration of the retina when its venous return is obstructed by increased pressure of the intracranial fluid. Though this process is universally recognized, it is curious to note the opposition to the hypothesis that a similar obstruction by increased hydraulic pressure may occur *in utero*.

There are two results of this obstruction:

(*a*) The muscles naturally fail to develop properly.

(*b*) There is a thickening and stiffening of the fibrous tissues around the joints, which is not easy to explain.

The study of contractures of this kind involves the investigation of the mechanical conditions of the pregnancy that produced them. This line of research is neglected in the present very fragmented state of medicine, as it involves the territory of two definitely divided and firmly "closed shops", those of orthopædics and obstetrics. It will be found by anyone undertaking it that the results confirm the working hypothesis upon which it is based.

Hydraulic compression would, of course, affect all four limbs equally, the effects being more severe the further the tissues involved lie from the pump of the heart. A significant proportion of these children will be found to have pregnancy histories of hydramnios; and often they emerge from the uterus stiffened in a form that could only be possible in a cavity of abnormal size; e.g. with extended hips.

Those, on the other hand, who have developed in a cavity too small for them will have the compression effects confined to those parts which are unsheltered; most often, of course, the legs and feet. Usually the arms escape, being sheltered by the huge fœtal head; but rarely they may be caught in the "wooden soldier" position, straight down alongside the body. The mothers give pregnancy histories of the kind that may be expected, these being particu-

larly valuable if they have experience of a normal pregnancy for comparison. They are small in the later months, often remarking that "all the neighbours were surprised when I had a baby"; and, in addition, nearly always are very uncomfortable.

Treatment: Treatment of contractures of this type consists mainly in cherishing and preserving the deficient muscles. The mistake is not infrequently made of attacking such structural deformities as flexed wrists and knees without considering that the real trouble is not the structural deformity, but the lack of function. These joints respond very badly to manipulations followed by immobilization in plaster of Paris; though it is possible to improve the position in this way the deformity steadily recurs, while the immobilization has inevitably weakened the muscles.

Extrinsic

Leaving out such rare and intractable conditions as webbing of the limbs at the elbows and knees, the important contractures in children are those which are due to malposition *in utero*, that is to say that the child has been lying in an abnormal position. Two of the three stock varieties of moulding deformities of the feet, club-foot and metatarsal varus, belong to this category; the third, metatarsal valgus, is due to mechanical compression in the normal position. A most important member of the first class is what I call congenital postural scoliosis, due to the child lying with the spine bent sideways *in utero*. The amount of the contractures in this condition can be best demonstrated by X-rays taken in three positions. The first is with the child lying as he does when contentedly at rest. The second shows him with the spine bent as far as it will go in the direction of the curve, and the third shows the curve corrected as far as possible. It is urgently necessary to diagnose and correct this deformity before the child begins to sit up and walk; or else the combination of body weight and unbalanced muscular action will cause a rapid and accelerating increase of the curve into the most intractable and crippling condition of "idiopathic scoliosis". In my opinion idiopathic scoliosis is a missed congenital scoliosis.

Acquired Contractures

The most important of these contractures are due to unbalanced muscular action, caused either by cerebral palsy or by poliomyelitis. The commonest crippling effect is the setting down of the foot into equinus. In cerebral palsy this is due to the excess of power in the muscles of the calf over those which dorsiflex the foot; in poliomyelitis to the very common paralysis of the peronei and extensors of the ankle. In both cases these factors are reinforced by the action of the bedclothes in pushing the feet downwards and inwards. One of the most important of the many gaps in classical splints is the lack of one to counter this equinus, the commonest of all elements in deformities of the feet. I have designed an "equinus splint" which can be worn at night; if it is not altered too far from its original design it will be found effective. Applied early enough it will avoid the only too common fixed deformity, which should never be allowed to occur. It is worth mentioning that many centres for the treatment of cerebral palsy do not draw a sufficient distinction between a spastic and a fixed equinus; one can see attempts to get a child to "relax" an ankle which is firmly fixed by acquired contractures round the joint. My treatment for ankles in this state is to work them up gradually into calcaneus by a series of walking plasters applied without an anæsthetic, and when a satisfactory range of movement upwards has been attained, to keep it by means of the equinus night splint. I thoroughly dislike the common tenotomy of the tendo achillis; it is so easy to do too much or too little.

Joint Contractures

By Trevor H. Howell, F.R.C.P.Ed.

When the former municipal infirmaries for the chronic sick were taken over under the National Health Service, several surveys were carried out by teams of observers. Perhaps the best known of these were by Professor A. P. Thomson in Birmingham and by McEwen and Laverty in Bradford, all of whom were surprised to find joint contractures in a large number of bedridden patients. Professor Thomson remarked in his Lumleian Lecture of 1949: "We speculated much about the cause of this condition which I had never encountered before. . . . The contractures to which I would draw attention are usually found in very old people who have been long in bed. The posture is one of extreme flexion; the knees are drawn up to the abdomen, the heels touch the buttocks, the arms are held close to the mouth and the chin rests on the chest. The wrists and fingers are sometimes freely movable; when feeding, either hand is used to stuff food into the mouth without the help of a spoon or fork. Such patients are difficult to examine. Left to themselves they pull the bedclothes over their

faces and lie motionless for hours. In all that we have examined, we have found the plantar responses flexor, but it was hardly possible to be certain of the tendon reflexes. Rough testing of sensation showed no gross change, but vibration sense was absent."

McEwan and Laverty (1949) found joint contractures in 524 out of 700 patients whom they examined. They noted that these changes occurred with great frequency in conditions limiting or preventing movement in the limbs such as arthritis or cerebral thrombosis.

Types of Contracture

Those of us who work in hospitals for the chronic sick are often asked to see patients with joint contractures or flexion deformities with a view to advising on their treatment. Since such cases have usually been neglected for some years previously, this is often a very difficult problem. During the last ten years I have made a study of contractures at St. John's Hospital, Battersea, and at Queen's Hospital, Croydon, which between them serve nearly half a million people. Observation of a number of such joints has allowed their separation into three different groups:

(1) Postural contractures.
(2) Contractures due to chronic arthritis.
(3) Contractures due to disease of the central nervous system.

Each of these groups is an entity on its own and shows a different response to treatment. This was recently confirmed by the American trials of the drug zoxazolamine and by my own experiments with other relaxants and with ultrasonic radiation.

Postural contractures are the consequence of maintaining a flexed position in bed, under-treatment, and a desire by the patient to withdraw from the world. The skeleton of such cases usually shows considerable decalcification but the articular changes are not, as a rule, marked. Old people of this kind resist any attempt to move their joints; but in the early stages vigorous treatment can overcome the tendency of flexion deformity if the patient will co-operate.

One woman of over 80 years of age, living in a workhouse, took to her bed and there proceeded to curl up. She objected to being moved or washed and refused to straighten her legs. Within two years there was such shortening of her hamstrings and wasting of her quadriceps that she possessed a fixed flexion deformity. The left arm was also held close to the mouth and the chin rested on her chest.

Another type of postural contracture may occur in association with chronic ulcers of the feet or legs. If patients with such lesions are allowed to stay in bed for long periods, they assume a flexed position of the lower limbs. After a time, the hips and knees become relatively fixed in flexion while the patella may even become adherent to the femur. Eventually a definite contracture occurs which prevents the patient from standing or walking.

Joint contractures in arthritis.—In the course of rheumatoid arthritis the patient tends to get into a vicious circle of joint pain, muscle spasm, and immobility in a position of flexion. This eventually gives rise to a condition in which the flexor muscles become hardened and thickened through continuous spasm. The corresponding extensor muscles are thin and wasted. Around the joints themselves, the inflammatory products favour fibrous deposition, so that the peri-articular and articular layers of tissues get inextricably mingled together. It is possible for the ends of two bones to become fused so that it is not possible to see where they have joined. Such bones also have a very thin bony cortex and are particularly liable to snap if moved forcibly.

However, flexion deformities do not constitute all the contractures occurring in chronic arthritis. There is often an element of adductor spasm as well as flexor hypertonus: and the distal part of the extremities may develop all kinds of bizarre muscle pulls. This was first mentioned by Charcot (1881).

Different joints have different tendencies when they become the seat of contractures. The cervical spine usually bends laterally and this deformity may be so marked as to cause bedsores of the pinna. The shoulder-joint often develops an upward subluxation of the humerus which prevents adequate abduction of the arm. This syndrome was described by Howell (1950). The bones, ligaments and soft tissues become fused, so that any abduction of the arm is performed by movement of the clavicle and scapula.

Elbows: When the elbow-joint is the seat of contracture, it becomes flexed and cannot be fully extended. Sometimes there appear to be considerable bony deformities, chiefly affecting the lower end of the humerus and the upper part of the ulna and radius. In a long-standing case bony ankylosis takes place. There may be some upward or backward displacement of the ulna, which can actually perforate the lower end of the humerus to cause an immobile fixed joint deformity.

Carpus: The changes in the carpus due to rheumatoid arthritis, are, of course, well known

and will not be described further. The point of interest is to note that marked structural anatomical change may not greatly impair function.

Fingers: It is difficult to formulate an adequate classification for the deformities of the fingers due to rheumatoid disease. The general tendency to ulnar deviation and the frequency of generalized flexion has been frequently described. But there is also a group of patients with hyperextension of certain joints, usually the proximal interphalangeal articulations. At times flexion of the more distal joints may be combined with extension of the proximal joints but the distribution of the contractures is capricious.

Hips: In the lower limbs, the hips are rarely affected by rheumatoid arthritis, but many patients showing rheumatoid changes in other joints have osteoarthritis of the hips. Some of these develop an "excavated acetabulum". If these patients are allowed to become immobile, the spasm of their flexor and adductor muscles produces a contracture of the hip with secondary flexion and adduction of the knees. The deformity tends to become progressive and, as a result, the inner aspects of the knees approximate and press upon each other. This leads to necrosis and ulceration. At other times, the heel of one contracted leg may press upon the other with such force as to break the bones. In consequence, compound fractures may result and these are particularly difficult to treat.

Knees: The main deformity of the knee is caused by shortening of the hamstrings. This first produces flexion of the joint, which becomes immobilized by fibrosis. Later, the head of the tibia may be drawn backwards behind the lower end of the femur as soft tissues, capsule and ligaments are destroyed. Such a subluxation causes undue pressure in the popliteal space upon nerves and vessels. In consequence there ensues marked œdema of the foot together with trophic disturbances. This train of events, it will be seen, is all the result of spasm of the flexor muscles and corresponding wasting of the extensors. Another factor, which often hinders effective treatment, is the liability of the patella to become adherent to the articular anterior surface of the lower end of the femur. This, by mechanical means, prevents full extension of the joint and thereby favours a flexed position.

Ankles: The deformities of the ankle in rheumatoid arthritis may be due to poor muscle tone and the bed-fast state when dropped foot and external rotation are found. At other times the foot is fixed at a right angle to the lower leg. Alternatively, a combination of the two may be found with foot drop and fixation both existing.

Neurogenic contractures.—The most frequent cause of neurogenic contractures is cerebral thrombosis, followed by hemiplegia. This gives rise to flexion deformities on the affected side, chiefly involving the knee, wrist and elbow. Similar deformities may occur in the course of untreated subacute combined degeneration of the cord, disseminated sclerosis, or be a rapid complication of certain forms of encephalitis.

When the contracture is due to disease of the central nervous system, the dysfunction is usually a simple hypertonus of the flexor muscles. Sometimes, however, there is also an element of adduction, particularly at the shoulder- and hip-joints. At the ankle-joint, weakness of the anterior tibial muscles may give rise to a form of foot-drop, with some inversion, in bed-fast patients. With some long-standing examples of hemiplegia, the tendons causing dorsiflexion of the toes tend to become taut. This may cause the phalanges to ride up on top of the metatarsal heads. One consequence of this is to make the plantar responses hard to elicit.

It should be noted that contractures of neurogenic origin are often associated with trophic changes, such as œdema of the feet. For this reason, it is dangerous to employ splinting in an attempt to correct deformities of this origin. The continued, and often increasing, muscle hypertonus sometimes forces the edge of a splint into the devitalized tissues. This can give rise to ulceration, necrosis and even gangrene.

Treatment

The treatment of a joint contracture, and the likelihood of success, depend chiefly upon its origin. Postural changes seem to depend upon the mental attitude of the patient. If an old woman is determined to curl up and hide away from the world, like an animal, no physical treatment is likely to help her.

Neurogenic contractures have their origin in damage to the central nervous system. Until recently, it has not seemed possible to affect them by drugs. But reports on the use of zoxazolamine (Flexin) combined with chlorpromazine suggest that progress may now be possible on these lines. Surgical methods, such as tenotomy or capsulotomy, have a limited place in patients with ability to co-operate. The danger is to cut too far or too deep, leaving a flail limb after the operation.

Arthritic contractures, in my experience, pass through three separate stages before becoming established. The first stage is that of simple reflex muscle spasm, arising from an inflamed and painful joint. This usually produces an attitude of flexion, with some

wasting of the extensor and abductor muscles as first described by Charcot (1881). The second stage shows the deposition of inflammatory products within and around the joints which tend to become organized and produce fibrosis. The third stage is one in which the bony changes predominate. Ankylosis, subluxation and osseous deformity now produce a mechanical obstruction to movement.

The first phase of the contracture is compounded of inflammation, pain, and muscle spasm. The sequence of events may be interrupted at any of these three points, either by general measures or by local treatment. For example, intra-articular injection of hydrocortisone will often diminish the inflammation and thereby stop the formation of a contracture. Injection of procaine will lessen the pain, thus relaxing the muscle. Injection of 0·5 mg. of Prostigmin can relax the muscles which are in spasm, thereby lessening the pain and disability. Similar results may also be obtained by various forms of physiotherapy.

In the second stage of contractures we have as our chief difficulty the presence of fibrosis and adhesions. It is usually necessary to break down these by some form of manipulation. The best results, as a rule, are achieved under local anæsthesia attempting only a small amount on each occasion. If too much is attempted, as is the danger under general anæsthesia, there may be either an exacerbation of the original arthritis or extensive bruising. Both of these cause pain to the patient and make him more unwilling than ever to move the joint.

The third stage of contracture is that of bony deformity and ankylosis. If manipulation under general anæsthesia is attempted during this stage there is a serious danger of fracture of the long bones with considerable shock to the patient. So far, no effective method of treating this stage has been discovered.

Ultrasonics.—We have recently been employing ultrasonic radiations in an attempt to reverse the changes which produce contractures. This followed the demonstration by Curwen (1953) that this form of energy softened scar tissue. The machine used was the "Ultrasonar" made by Nordelectro. It had two treatment heads, one for deep treatment and the other for superficial treatment. Only the latter was used in this investigation. Our routine was to employ a dose of 5 megacycles for five minutes. Joints which were easy of access were treated by movement of the head through a film of liquid paraffin. Others, more difficult to approach, were treated through a small rubber "water bag" made from a condom. Treatment was given twice weekly to one joint at a time. After each exposure to ultrasonics, the range of movement was measured by a goniometer. In the present series, bilateral lesions were selected, so that one joint could act as control for the other.

The first patients treated by ultrasonics had advanced contractures due to rheumatoid arthritis. The results were rather disappointing. Only a very few degrees of added mobility were obtained in these cases. Further investigation showed the presence of bony deformities in the joints. It was this discovery which led to the conception of the different stages of an arthritic contracture.

Later, we selected twenty joints whose contractures were in the second stage (fibrosis). Here the results obtained were much better. As may be seen from Table I, only two joints

TABLE I.—EFFECT OF ULTRASONICS ON ARTHRITIC JOINT CONTRACTURES (GRADE 2)

Case	Joint	Increase of movement (Degrees)	Control joint	No. of treatments	Comments
1	Knee	10	No Change	3	(Fixed patella)
2	,,	23	,, ,,	6	
3	,,	17	,, ,,	4	
4	,,	15	,, ,,	3	
5	,,	17	,, ,,	4	
6	,,	15	,, ,,	4	
7	,,	7	,, ,,	2	(Discharged home)
8	,,	20	,, ,,	4	
9	,,	17	,, ,,	5	(Control joint increased flexion)
10	,,	20	,, ,,	5	
11	,,	15	,, ,,	5	
12	,,	10	,, ,,	3	
13	,,	15	,, ,,	18	(Irregular out-patient attendance)
14	,,	4	,, ,,	4	(Fixed patella)
15	,,	2	,, ,,	3	(Fixed patella)
16	,,	33	,, ,,	6	
17	,,	20	,, ,,	4	
18	,,	14	Increase in extension	4	(Control joint improved)
19	Shoulder	5	No Change	6	(Movement looser within range)
20	Hip	30	,, ,,	3	

failed to show an increased range of movement. Even more striking was the improved freedom of movement within that range. This was usually maintained after the cessation of treatment and did not regress in the patients whom we followed up. The additional range of joint mobility varied from 7 degrees to 33 degrees. It was usually obtained by the early treatments. After the sixth exposure, no further amelioration normally took place. In only one patient did the untreated control joint show any improvement during the experiment. All the rest showed no alteration of mobility.

On the other hand, when we studied the behaviour of neurogenic contractures, we observed an interesting phenomenon. During the actual period of treatment, the tight flexor muscles of a hemiplegic limb relaxed and the limb could be extended. Yet, five minutes after exposure to ultrasonics ceased, the muscle spasm returned and the limb resumed its contracted position. The ultimate, permanent result was little or no increase in mobility. In 3 patients with stiff painful shoulders after a cerebral thrombosis, loss of pain and increased mobility were observed. But flexion deformities of arm or leg remained only temporarily relaxed in all 15 cases of neurogenic contracture.

Up to date, we have been unable to treat any postural contractures on account of lack of co-operation by the patients.

Discussion

Since, as McEwan and Laverty (1949) showed, joint contractures are one of the common causes of the bed-fast state, it is most important to prevent them whenever possible. At present, the mechanism of the flexor hypertonus which forms their basic pathology is only imperfectly understood. But our observations described above make it clear that encouragement of extensor movements and electrical stimulation of extensor and abductor muscles can play an important role. When spasm is secondary to chronic arthritis, the use of Prostigmin injections together with physiotherapy can often prevent the stiffening which is the precursor of the second stage (fibrotic) contracture. We have also experimented with the use of Prostigmin in a vanishing-cream base, which the patients can rub in daily themselves. Our preliminary results have, on the whole, been encouraging. One or two subjects, however, complain that the use of this cream makes their gut over-active.

The results of ultrasonic radiations will need further study. Their beneficial effect upon periarticular fibrosis seems quite definite. But the unexpected temporary relaxation of hemiplegic contracture is a phenomenon of an unusual kind. No mention has been made of the pain-relieving properties of ultrasonics in certain cases since that has no connexion with joint contractures.

At present, the third stage of arthritic contractures with bony abnormalities remains unaffected by any known form of treatment. It is, therefore, important to prevent its formation by active measures in the earlier stages, otherwise these patients become exceedingly difficult to nurse effectively, and often suffer a great deal of pain.

Summary

The study of patients with contractures of their joints allows them to be divided into three separate types—those due to posture, those due to arthritis, and those due to lesions of the central nervous system.

Arthritic contractures pass through three successive stages of muscle spasm, fibrosis and bony deformity. The course, prognosis and treatment of each is discussed.

A description of the results obtained from the use of ultrasonic radiations in these conditions is given.

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Section of Experimental Medicine and Therapeutics

President—Professor C. A. KEELE, M.D., F.R.C.P.

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DISCUSSION ON HYPOTHERMIA

Dr. E. Neil (Middlesex Hospital Medical School): *Sequelæ of Circulatory Arrest during Hypothermia.*

Hypothermia is used by the cardiac surgeon so that the circulation may be interrupted for a longer period to allow operation within the dry heart. The period of circulatory arrest at 26° C. which is regarded as safe has been given as ten minutes by Swan and Ross. Most workers seem to have been preoccupied with the ability of the various vital organs to resist anoxia alone and few have paused to think of the congestive effects of complete venous occlusion for an extended period. When such congestion is associated with anoxia the effects may be serious.

One way of following the progress of an animal or a man subject to the full ritual of the hypothermic cardiac operation is to study the acid-base equilibrium. If blood is equilibrated *in vitro* at 37° C. with various CO_2 tensions the pH of the equilibrated blood can then be measured at 37° C. If the pH values obtained are plotted against the logarithm of the CO_2 tensions, the relationship is linear. If the procedure is repeated with samples of the same blood equilibrated at 26° C. and the pH values measured at 26° C., the points obtained fall on exactly the same line as before. It follows from this that if blood is removed from an animal at any stage of cooling or re-warming, this blood can be equilibrated with a series of CO_2 tensions *in vitro* and the corresponding pH values can be measured at any one temperature, say 26° C. If there has been no development of metabolic acidosis then the various blood samples removed should give the same log. pCO_2/pH graph. If there *is* metabolic acidosis, however, the log. pCO_2/pH line will be displaced to the left so that a given pCO_2 will be associated with a lower pH. We therefore used this method in experiments *in vivo*. Dogs were cooled under artificial ventilation to 26° C., their chests were opened and their venæ cavæ were occluded for ten minutes. Following this the circulation was re-established, the chest was shut and the animals were re-warmed. Blood samples were taken, before cooling, after cooling (pre-clamp samples), at the end of clamping off the circulation for ten minutes (post-clamp samples) and on completion of re-warming. All these samples were equilibrated with the series of CO_2 tensions at 26° C. and the pH of the equilibrated samples was read at this same temperature. The results of experiments on 26 dogs showed that after circulatory arrest for ten minutes the "post-clamp samples" revealed a very obvious metabolic acidosis. This "post-clamp" acidosis, revealed by the log. pCO_2/pH graph, became worse during re-warming. Similar investigations were made on patients undergoing cardiac surgery under hypothermia, thanks to the co-operation of Sir Russell Brock. In some cases gross acidosis and lactacidæmia were found on re-warming.

We attribute the derangement of acid-base equilibrium to the effects of venous congestion and anoxia during the occlusion period. The central venous pressure was measured in many of our dog experiments and on shutting off both venæ cavæ this pressure rose sharply to levels of 25 cm. H_2O or more. The high pressure was well maintained during the occlusion period. After seven minutes of circulatory arrest blood withdrawn from the venous catheter showed a negligible content of oxygen.

Liver structure was examined histologically. After cooling and re-warming (without operative intervention in the chest) the liver structure appeared virtually normal. On the other hand after cooling with circulatory arrest followed by re-establishment of the circulation and re-warming, liver structure was grossly deranged. Centrolobular necrosis with extravasation of blood was obvious. Galactose clearance studies were performed on both series of dogs. After cooling alone, galactose clearance was reduced to about a third of normal, but on re-warming the clearance recovered to 80% of its pre-cooling value. After cooling plus circulatory arrest for ten minutes, followed by re-establishment of the circulation and re-warming, the galactose clearance after re-warming showed no improvement on the rate observed when the body temperature was 26° C.

Prevention of congestion during circulatory arrest was practised in two ways in additional experiments. (1) By aspiration of blood from the inferior vena cava into a silicone reservoir. (2) By pumping the blood from the vena cava into the arteries.

By either of these methods the central venous pressure can be prevented from rising during occlusion. The results of both measures were similar. The dogs showed normal liver structure and galactose clearance after re-warming and the metabolic acidosis seen after release of the venæ cavæ almost disappeared during re-warming.

These results are presented in extenso elsewhere (Brewin *et al.*, 1955).

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Dr. B. G. B. Lucas (Surgical Unit, University College Hospital Medical School, London) discussed the practical side of hypothermia, how to cool the patient, where to record the temperature, and how far the temperature should be reduced (Lucas, 1956). He said that the time available for circulatory occlusion at low temperature had not yet been established satisfactorily, but a safe guide was five minutes at 28° C., with an increase of one and one-half minutes for every further one degree fall. This factor was modified by age, and by the state of the brain and the heart immediately prior to the circulatory occlusion.

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LUCAS, B. G. B. (1956) *Proc. R. Soc. Med.*, **49**, 345.

Mr. D. N. Ross (Guy's Hospital): *Problems Associated with the Use of Hypothermia in Cardiac Surgery.*

My remarks largely corroborate those of Dr. Lucas in that we have been able to use hypothermia as a safe and practical procedure without serious sequelæ such as those Dr. E. Neil has mentioned. Most of our cases have been adults; whereas Dr. B. G. B. Lucas has more experience in the younger age groups. Our experience in 70 patients subjected to hypothermia with complete arrest of the circulation for five to ten minutes has enabled us to appreciate and to eliminate many of the difficulties and dangers of the technique. The main hazard, as far as we are concerned, has been from anoxic brain damage during the period of circulatory arrest although the many alterations in physiology and the disturbing tendency of the ventricles to fibrillate have often diverted our attention from the brain. Thus we have had 26 cases of ventricular fibrillation during the cooling or intracardiac surgery with complete recovery in 21, but where we have had an absent or poor cerebral circulation for more than ten to twelve minutes there have only been 5 recoveries out of 18 cases.

The prevention of brain damage is, we believe, dependent upon the temperature to which we can cool and the period of permissible circulatory arrest at that temperature. In practice, the lowest temperature we can attain with safety is limited in our present technique by the onset of ventricular fibrillation. In dogs and in humans, there is very little tendency to ventricular arrhythmias above 28° C. although atrial fibrillation is common around 32° C. in humans. Between 28° C. and 25° C. there is a sharp increase in the incidence of ventricular arrhythmias, ectopic beats and A-V dissociation and if the heart is mechanically stimulated at these temperatures, ventricular fibrillation is likely. Below 25° C. ventricular fibrillation is very common and is likely to arise without an extraneous stimulus. Consequently we no longer cool adults below 28° C. and in children, whose hearts seem more resistant to ventricular fibrillation, we try not to cool below 26° C. (Fig. 1). Since adopting this simple policy our incidence of ventricular fibrillation during cooling has dropped precipitately.

We have given up chemicals like Prostigmin as a method of preventing fibrillation since we have not been convinced of their effectiveness. We do try, however, to minimize all forms of trauma and avoid handling the heart during the cooling. Again after the period of arrest of the circulation we are very aware of the danger of suddenly increasing the work of the anoxic myocardium and for this reason, the venæ cavæ are released slowly and in turn to allow the heart to accommodate to the increased load. We have not found any special difficulty in electrical defibrillation of the cold ventricle provided adequate cardiac massage is used to restore myocardial tone, before using the defibrillator. Too much reliance is often placed on the ability of this machine to revert the rhythm in an atonic, anoxic and poorly contracting ventricle, whereas its true function is to depolarize the well-oxygenated and vigorously-contracting heart muscle. Where defibrillation has been unsuccessful it has generally been due to serious damage to the valves or conducting bundle as a result of surgery or an inability to repair the defect.

The cause and prevention of ventricular fibrillation have received a great deal of attention in hypothermic literature and at varying times an acidosis, a rise or fall of potassium or the prolonged systolic activity phase of the cold ventricle or falling coronary circulation have been inculpated. Whatever the mechanism, we cannot escape the fact that it is the effect of cold on the active working ventricles which is ultimately responsible since it is a daily

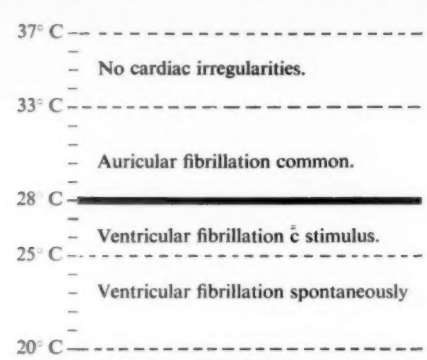


FIG. 1.—Cooling zones in relation to cardiac arrhythmias.

experience in cardiac surgery to find the heart at normal temperatures amazingly tolerant to surgical, pharmacological and metabolic insults of a very severe nature with only trivial disturbance of rhythm or function.

A feature of hypothermia which has been stressed is that while the metabolism and activity of the tissues decline steadily with cooling, the heart alone continues to contract and extract oxygen at a disproportionate rate. Also in both surface and blood-stream cooling methods, it is the active heart which is likely to be the coldest organ in the body since it is required to distribute the cold blood coming from the surface tissues or cooling coil to the deep tissues and brain. Consequently the heart is both the most active tissue and at the same time the coldest. We can separate these factors of activity and cold by inducing hypothermia with the aid of a heart-lung circuit so that the heart is relieved of its work load. Under these circumstances the heart slows progressively and is arrested in asystole at about 14° C. without passing through a phase of ventricular fibrillation. The heart is then cooled via its arterial supply to very low temperatures and this is achieved by permitting its work to decline like the rest of the body with falling temperature. Hypothermia has been induced in this way by Gollan *et al.* (1955) with the aid of a simple heart-lung machine and temperatures of 0° C. have been reached with recovery. However, the problems associated with artificial pumps and oxygenators at present outweigh the advantages of this theoretically ideal cooling technique. When it can be applied with safety it will permit very rapid cooling to much lower temperatures with correspondingly longer periods of time available for intracardiac surgery. Also these low temperatures will confer the advantage of an arrested and quiescent heart.

The permissible period of total arrest of the circulation under hypothermia.—We are, at present, limited here by the time we can safely exclude the brain at our working temperature of 28° C. Oxygen consumption studies and experimental observations in dogs suggested a safe period of occlusion of at least fifteen minutes at 25° C. and at 28° C. we have allowed ourselves a maximum of ten minutes of circulatory arrest with about eight minutes of intracardiac surgery. This has proved safe in practice and although we have had complete recovery in an adult woman who had her circulation arrested for thirteen minutes at 28° C., there was definite evidence of disturbed cerebration for forty-eight hours post-operatively. Signs of anoxic brain damage in the post-operative period have been an initial difficulty in re-warming followed by hyperpyrexia and a cold pallor of the skin associated with fixed dilated pupils. These patients have never recovered. Milder signs have been a delay in coming round from the anæsthetic, restlessness and a sharp rise of temperature to 103–104° F. In these cases we have taken precautions to limit fluids, particularly blood replacement, and we have occasionally given hypertonic solutions, in addition. In fact we aim to undertransfuse in all cases. Evidence of brain damage is not seen in cases which are cooled to 28° C. and have less than ten minutes of circulatory arrest. These cases come round from the anæsthetic promptly and often while the body temperature is still about 33° to 34° C. Also there is generally no post-operative rise of temperature.

The eight minutes of intracardiac surgery limits us in the type of intracardiac defect in which we can hope to achieve repair. Straightforward defects of the atrial septum fall into this category and also pulmonary valvular and infundibular stenosis and more recently aortic valve stenosis. Ventricular septal defects including Fallot's tetralogy and the ostium primum type of atrial septal defect are not suitable for closure by present techniques; not because they may necessitate an incision in the ventricle—for ventricular incisions can

be well tolerated in hypothermia—but because at least twenty minutes of unhurried cardiac surgery are required for their definitive closure.

A difficulty we have encountered with the venous blood-stream cooling technique has arisen as a result of the very rapid cooling rate we have been able to achieve especially in small children. Unless the rate of cooling is deliberately kept within certain limits, uneven cooling of the body will result in very low heart temperatures and the danger of ventricular fibrillation before the mass of the brain has cooled evenly. For this reason we aim to cool at a rate of not more than 1° C in four minutes for children and infants below 26 kg. making a total cooling time of about thirty-six minutes. The cooling rate is charted at five-minute intervals during the lowering of temperature so that adjustments can be made to keep the rate of fall approximately along a predetermined line on the graph. Adults generally cool at a rate of 1° C in six to eight minutes with a cooling time of about forty-five minutes. Too rapid a cooling rate is also reflected in the ECG picture which shows atrial fibrillation and A-V conduction disturbances. An ominous development has been an increased notching and slurring of the Q.R.S. The interpretation of this phenomenon is under debate but it often precedes the development of ventricular fibrillation.

We have found the blood-stream method of cooling has great advantages in cardiac surgery, particularly in allowing us to manipulate the heart freely and to take pressure measurements and explore the interior of the atria digitally at normal temperature and when the heart is not irritable. This ability to make a final diagnostic assessment at operation will assume increasing importance when we have a heart-lung by-pass available. A choice of either hypothermia or the artificial heart lung will then be applied to meet the appropriate needs of the intracardiac defect.

Difficulties which we had anticipated as arising from altered or disordered metabolism have not constituted a problem in clinical practice. We aim to keep the respiratory acidosis at a minimum by the anæsthetist maintaining a more than average respiratory exchange throughout the hypothermic period without sudden bursts of hyperventilation—as has been advocated by some workers. For the rest, we feel that the total time during which the body is subjected to a low temperature is important. This is achieved by rapid cooling followed by rapid blood-stream re-warming. Once the temperature is restored to normal, we assume that the kidneys and liver will again be able to make good any biochemical disturbances that may have developed and our cases now have the same pre- and post-operative management as any major chest operation.

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Dr. H. H. Khalil (University Hospital, Alexandria, Egypt) described results obtained using the intra-gastric balloon (Khalil and Mac Keith, 1954) for producing hypothermia by internal cooling. He described a machine for continuous controlled perfusion of cold water. The rate of production of hypothermia was controlled by the rate of flow of coolant into the intra-gastric balloon. The degree of distension of the stomach by the balloon was under continuous observation in preliminary experiments.

In preliminary experiments at Guy's Hospital in 1954, using this method he had lowered the temperature of rabbits from 39° C. to 20° C. and the heart beat had slowed to 60 beats a minute. Later the method had been used in a case of hyperpyrexia in a child (Khalil and Mac Keith, 1954).

Dr. Khalil described a further series of experiments on dogs under anæsthesia and cooled by continuous flow through the balloon of two litres per minute of water at a temperature of 4° to 5° C. This gave lowering of the body temperature to between 23°–26° C. rectal temperature. The time taken for this cooling was about two and a half hours. Shivering was prevented by the animals being under ether anæsthesia. After cooling was stopped, there was a further drop in rectal temperature and heart-rate. When no warming was applied animals cooled only to 25° C. warmed much more rapidly than those who had been cooled to 23·2° C. Recovery could be accelerated by circulating warm water. There were no signs of permanent damage from these procedures which probably act mainly by slight cooling of a large volume of blood circulating in the great vessels of the abdomen.

In contrast to the results described by Mr. D. N. Ross and illustrated by his Fig. 1, Dr. Khalil had found that after internal cooling, arrhythmias were rare even at 23° C., the injury potential described (Osborne, 1953) as precursor to ventricular fibrillation appeared in only 4 cases out of 16, and ventricular fibrillation did not occur at all.

Internal cooling by the intra-gastric balloon is an efficient and a safe technique.

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[For full Paper *see Lancet* (1957) i, 185]

Section of Psychiatry

President—WILLIAM SARGANT, M.A., F.R.C.P., D.P.M.

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Twenty Years of Leucotomy

By WALTER FREEMAN, M.D., Ph.D.

Formerly Professor of Neurology, George Washington University, Washington, D.C.

EGAS MONIZ died a year ago at the ripe age of 81. He lived to see one of his major discoveries, angiography, universally adopted and the other, leucotomy, still in vigorous dispute. Fulton, Tow and others have told how the idea of leucotomy germinated here in London. At the Second International Neurological Congress in 1935 the session on the frontal lobes brought forth a number of reports of the harmful effects of traumatic and neoplastic lesions upon personality. Moniz, having already pondered the neurology of obsessive thinking, was the only one present who saw through these damaging effects to their possible benefit in cases of functional mental disorder. A year after the Congress he reported twenty leucotomized patients; one-third recovered, one-third improved and one-third unchanged. It is remarkable that over the past twenty years the proportion of good results has remained much the same.

The work was taken up, on a small scale at first, in Cuba, Brazil and Italy. In the United States it took Freeman and Watts five years to collect the first hundred cases. It may be recalled that the various shock therapies were flourishing in this same five-year period. The Board of Control assembled 1,000 leucotomy cases in 1947. The U.S. Public Health Service survey in 1951 counted 18,600 psychosurgical cases covering the fifteen-year period. Was this an unhealthy growth? In the years 1949–1951, according to the survey, the leucotomy rate in the U.S. was 6·5 per 1,000 average daily resident patient population. Unoperated patients, therefore, averaged 993·5 per thousand. At this rate it would take some 150 years to apply leucotomy to everybody, not to mention later arrivals. Leucotomy has been applied, it would seem, on a rather modest scale. Recently interest has veered to the tranquillizing drugs. It may be several years before the proper indications for leucotomy are fully established. Meanwhile it may be of value to review the twenty years of leucotomy in an effort to determine the place that it deserves in psychiatric therapy.

INDICATIONS AND CONTRA-INDICATIONS

Leucotomy achieves its most satisfactory results in patients who are distressed by feelings of anxiety, obsessive thinking and what may be termed anguish or tortured self-concern. The operation reduces the emotional tension to a point where it no longer disables the patient. The list of disorders for which it has been successfully employed is a long one,

and embraces not only certain psychoses and psychoneuroses, but also psychosomatic disorders and pain syndromes that can be relieved in no other way.

Heightened emotional tension is a *sine qua non* for success in leucotomy. Patients who have given up the struggle, who accept their symptoms as part of themselves, or who take refuge in alcohol or drugs are generally poor prospects for surgery. On the basis of several hundred assorted patients Watts and I concluded that a deteriorated schizophrenic looks and acts the same with or without his frontal lobes.

Experience has shown that leucotomy may be socially dangerous in patients with aggressive antisocial traits. There may be a difference between those who offend against property such as forgers, burglars and thieves as opposed to those who offend against persons. The almost complete absence of sex crimes by leucotomized patients is noteworthy. However, the time has not yet come when leucotomy can be recommended in the treatment of the sexual offender. Patients who commit crimes of violence under the influence of a psychosis are often favourable candidates. In another direction, leucotomy is to be undertaken with reluctance in patients with superior intellectual and social accomplishments. Artists, musicians, physicians, writers and ministers may lose some of their inspirational value as the result of their mental disorder combined with leucotomy.

When the pros and cons of leucotomy are being weighed in connexion with any given patient, the question must arise as to the possible damaging effect upon the personality, of the operation itself.

Is Leucotomy Harmful?

All but the strong proponents of the various psychosurgical operations will answer "yes". Theoretical considerations should make it so, since it is difficult to see how mutilation of the brain can make for better functioning. Even the proponents of operation are sometimes hesitant and apologetic about it, since they have seen many patients who, while being able to live more comfortably after operation, have nevertheless suffered some loss in depth of personality, some blunting of their creativeness, some decrease in sensitivity and empathy, some reduction in altruism, fervour, zeal or spiritual quality that they possessed at one time in their lives. These personality alterations are found so frequently in the run-of-the-mill patients after leucotomy that it has been rather widely accepted that the operated patient is different from his former self, and that, while he is able to live with himself and with others on a better plane than he could before he was operated upon, yet the intrusion of the mental illness plus the leucotomy has taken something away from him, something that was highly desirable as a social trait.

Psychiatrists who have carefully followed their patients over long periods can select a few who seem altogether unharmed by the operation and who manifest social poise, ambition, creativeness, executive capacity and altruism to a degree at least equal to their premorbid level. In fact, these patients accomplish more than might be expected precisely because they have been freed by operation from the burden of painful self-consciousness and sensitivity to criticism. They are able to direct their talents into productive fields beyond what had been possible for them before they fell ill. What they have lost through operation is the restraining drag of diffidence, the realization of the spread between ambition and accomplishment, and the hesitancy to undertake some constructive effort for fear of failure that would injure their self-esteem. The illness that led to disability and eventually to operation seems like an incident in the remote past. After convalescence they take up their lives as though the illness had never existed. They can even experience the same symptoms that they did during their illness, but no longer to the degree of ruminative incapacity.

Leucotomy does not necessarily interfere with progressive development of the patient's personality into a more mature and wholesome state. When the constructive aspects of the personality are overwhelmed by a disabling neurosis or psychosis, leucotomy can be undertaken with confidence that it will restore to the suffering patient the equanimity that is essential for further growth.

Five, Ten and Fifteen Years Post-leucotomy

The importance of long-range follow-up was stressed by Adolf Meyer on the occasion of the first presentation of the subject made by Watts and me in the fall of 1936. At that time we reported 6 cases operated upon within the preceding two months. Fortunately our selection was such that twenty years later we could say that 4 were successful. Had we selected a series of schizophrenic rather than mostly involutional or psychoneurotic patients

it seems likely that the question of leucotomy would then and there have been answered unfavourably.

From these 6 patients, the series grew to more than 600. All of the survivors have been traced for at least five years, and many of them for over ten years. Social effectiveness was chosen as the criterion of success. Patients were graded at various periods after operation, namely, employed, keeping house, home, hospital.

It requires about two years for the patient to become stabilized after prefrontal leucotomy. It is at this time that the patients who relapse are about balanced by those who improve slowly. Thereafter, for a period of many years there is substantial stabilization. This is shown in Table I.

TABLE I.—STATUS OF SURVIVING PRIVATE PATIENTS AFTER PREFRONTAL LEUCOTOMY

Diagnosis	Number	Employed %	Keeping house %	Home %	Hospital %
Schizophrenias					
2 yrs.	294	30	10	36	24
5 yrs.	285	30	10	30	30
10 yrs.	138	30	10	30	30
15 yrs.	26	23	15	35	27
Involutional depressions					
2 yrs.	112	10	46	34	10
5 yrs.	103	10	48	30	12
10 yrs.	74	2	48	32	18
15 yrs.	25	4	40	40	16
Psychoneuroses					
2 yrs.	101	44	21	29	6
5 yrs.	98	48	20	24	8
10 yrs.	76	50	17	24	9
15 yrs.	22	45	18	32	5

Similar stabilization is also noted in studies from the Boston Psychopathic Hospital, where the five-year results are rather better than those at the end of one year.

Comparison of patients operated upon as private patients and those operated upon in a public mental hospital (in this series, St. Elizabeth's Hospital), shows an immediate and striking difference. The number in the Freeman-Watts series is rather small, numbering 60 patients, and made up mostly of schizophrenics. Of the total number, 35% of the men and 45% of the women were out of the hospital for a period of more than six months. Detailed breakdown of figures is not worth while on such a small material but among schizophrenic patients, at least, there is a great difference, 60% remaining in the hospital as opposed to 30% of the private patients.

While the St. Elizabeth's patients were hospitalized longer on the average (6·5 years versus 3·5 years for the private patients), the support given by the family must be considered as of equal or greater importance in the outcome.

One of the controversial aspects of leucotomy is the question of when to perform the operation. There has been so much fear of producing unfavourable personality changes through operation that this is delayed until other methods can be thoroughly tested. This fear was only too well realized in the earlier years of the leucotomy research, but it seems adequately proven by this time that operation on the frontal lobes is not necessarily damaging to the personality.

Therefore, among the hazards of leucotomy, the greatest, in my opinion, is the hazard of delay. In speaking of topectomy and other psychosurgical operations less radical than standard leucotomy, Hoch and his collaborators have recently stated that: "The surgery need not be viewed as a desperate last resort after all possible measures of doubtful effectiveness or of known ineffectiveness have been tried. . . . An excellent therapeutic response may be obtained without the complication of undesirable personality change."

Granting the hesitancy to recommend leucotomy in a patient who is still functioning reasonably well, there are some clear indications for surgery: (i) First of all, I would place *relapse into disability*. There may be extenuating circumstances such as extreme external pressures that contributed to the relapse, and the psychiatrist is justified in repeating the treatment that previously aided the natural restorative powers of the patient. But relapse

shows that the patient is poorly armed to withstand the normal experiences of existence. Furthermore, repeated relapses are apt to lead to scarring of the personality that is even more serious than the mild effects of a leucotomy carried out conservatively before deterioration becomes noticeable.

(ii) The second indication for operation in my estimation is the *duration of the attack*. It is known that some patients can make an apparently perfect recovery after years of psychosis, but the number is small. On the basis of 25,000 first admissions, Malzberg states: "It is evident that the chance of discharge declines rapidly after two years of hospitalization." Granted that early treatment can restore a good 60% of patients (although relapses are threatened), there is another 40% of first admissions that do not stay well. It seems preferable to operate upon the patient who has shown unsatisfactory progress in the second six months, and take the small chance on something going wrong, rather than wait out the full two-year period.

Leucotomy and the State Mental Hospital

Duration of hospitalization is a factor of major importance in the outcome of leucotomy. Yet there are few data upon patients leucotomized after less than two years of hospitalization. When it is further considered that patients who enter state hospitals have already been treated on the outside until their disordered behaviour makes it necessary to send them to hospitals, it may be concluded that most of these patients are already in the chronic stage of illness. Review of their histories discloses an abundance of treatment for supposed physical complaints such as anæmia, back-strain, uterine retroversion, dyspepsia, and a variety of other manifestations that might well have been recognized as psychically determined years before the breakdown became evident. In various tabulations I have concentrated upon the time factor: *duration of symptoms*, *duration of disability* and *duration of hospitalization*. Of these three, the duration of hospitalization is the most important (Table II).

Table II.—Status of Survivors One Year after Transorbital Leucotomy Compared with Duration of Hospitalization before Leucotomy

Duration of Hospitalization	Number	Percentage released
None	22	77
Less than 6 months ..	88	82
6 months to 1 year ..	119	64
1 year to 2 years ..	176	52
2–3 years	173	44
3–4 years	97	39
4–5 years	92	28
5–10 years	289	26
10–44 years	320	12

I recently completed a study of patients operated upon by me in a number of state mental hospitals in different parts of the U.S. The release rate in these hospitals ranged from 0 to 91%. There were two hospitals where leucotomy was undertaken within one year, when other methods had failed. The release rates were 88% and 91%. Operation in the second year produced 60% releases. At the end of four years the figure was around 40%. It appears from these figures that early operation is justified. During the second year of hospitalization valuable time is being lost. If more conservative treatment is not producing results at the end of one year, it appears to me that operation gives the patient a greater chance of release than he will ever have again.

The West Virginia Lobotomy Project was undertaken in 1952 and continued during the succeeding two years. West Virginia is a mountain state with forests, mines and small farms, and some notable heavy industries. The state hospitals are above average in crowding. During the period of three years 744 patients were operated upon with a discharge rate of 36%. Based upon a *per diem* rate of $1.94, this represented a saving to the state of $337,000 (Table III). Of course, this was only a paper figure since, as Nature abhors a vacuum, the hospital population showed no decrease but, at least, other patients who needed treatment could be admitted to hospitals. During the first year there was a control group of 202 patients whose families refused permission for operation. At the end of one year 5 of these patients had left the hospital and 2 had died. Of the 228 patients operated upon in 1952, 85 left the hospital and 4 died. Of those discharged, the few who were employed had cash earnings exceeding the cost to the state of the whole project.

TABLE III.—WEST VIRGINIA LOBOTOMY PROJECT REPORT—JUNE 30, 1955
Transorbital Lobotomy Operations 1952, 1953, 1954

	Weston	Huntington Barboursville	Spencer	Lakin	Total
Number of patients operated on	222	153	225	144	744
Number released from hospital and still out	60	45	105	58	268
Improved sufficient for release but no home	9	0	6	62	77
Improved, but not sufficient to go home	29	46	19	18	112
Mental condition worse	31	2	6	0	39
Condition unimproved	84	53	87	3	227
Deaths	9	7	2	3	21
Patient-days saved	33,478	34,549	63,065	42,641	173,733
Budgetary savings	$56,243.04	$64,304.13	$111,163.13	$105,457.58	$337,167.88

And this did not include patients who were working on family farms, or keeping house, or otherwise usefully occupied.

It appears, then, that leucotomy can bring about release from the hospital of a considerable number of patients who can return to their homes and work productively.

The gain to the individual from leucotomy has to be considered in terms of relief of suffering, of restoration to productive existence, and to enhanced self-esteem. On all these counts leucotomy has accomplished more in a short time than any other therapeutic endeavour. It was also shown in this study that leucotomy by the transorbital route could be carried out in a situation marked by shortage of everything except patients.

These results are by no means unique. Transorbital leucotomy has been carried out in other state hospitals by Wilson *et al.*, by Moore, and by Jackson and Jako, all of them psychiatrists, upon more than 400 patients each, and with similar statistics. Substantially, they have found that transorbital leucotomy is a safe procedure to carry out in an institutional setting, that an over-all release rate of 35% is attained, and that the earlier a patient is operated upon the greater the chance of his being able to leave the hospital. The reduction of disturbed behaviour in those remaining in the hospital is frequently gratifying. Therefore, in spite of the offensiveness of transorbital leucotomy to the æsthetic sense of the surgeon, this operation offers much to patients and their families who would otherwise be denied a better chance for recovery and reunion.

There is also something to be said on the effect of long hospitalization upon the morale of the family. While the patient is at first in the hospital and undergoing treatments that have a good chance of restoring him to the family circle, the interest of the family is maintained on a high plane. When chronicity develops, the family attitude changes, the broken ranks are closed and the family goes ahead without the patient. At a much later date, should the patient be physically and mentally fit to resume family life, it is found all too often that there is no longer a place for the patient. The children have grown up, or the family has moved or split up, and the problem of his reintegration into the family circle has become more than a remote hazard. The best time to operate is during the first year, and the best time for release after operation is at the end of surgical convalescence. Then the patient and the family can get back to their readjustment problems in a more wholesome manner, and mutually obtain satisfaction in life together. Leucotomy can contribute notably to the morale of the whole family.

PSYCHOSOMATIC DISORDERS, TUBERCULOSIS, PAIN

(i) *Psychosomatic disorders* have been studied particularly by English authors, and a number of remarkable cures reported. The outstanding condition seems to be ulcerative colitis, but anorexia nervosa, Raynaud's disease, eczema, arthritis, spastic colon and many others have also yielded to leucotomy when medical and surgical measures have previously failed. The symptoms of hypertension are more likely to be benefited than are the blood pressure levels, but a decline in blood pressure in the middle-aged involutional depressive has often been witnessed, and this decline may last for a decade. Asthmatic states are less likely to be affected, and I have seen some instances in which asthmatic attacks have occurred for the first time following leucotomy. Peptic ulcer has been noted following operation, even with perforation, but in patients experiencing intractable pain its relief may be associated with healing of the ulcer. Leucotomy relieves preoccupation with the self and permits the organism to undertake the necessary repair.

(ii) Cheng, Tait and I have recently reported upon the beneficial effects of leucotomy in a series of 57 *psychotic tuberculous patients*. Not only did the patients gain weight and lose their fever, but the sputum became negative and the cavities tended to heal. Leucotomy permitted the patient to rest and to eat, and to accept treatment without the usual psychotic refusal to co-operate. Tuberculosis in a psychotic individual seems to be a strong indication for leucotomy if the course is downward in spite of medical and surgical therapy.

(iii) *Leucotomy in the patient who is experiencing intractable pain* is a knotty problem. Ten years ago Watts and I (Freeman, W., and Watts, J. W., 1946, *Proc. R. Soc. Med.*, **39**, 445) reported some cases before this Society. Further studies have shown that best results are obtained in patients who are emotionally upset by the pain, who require large to massive doses of opiates, and who do not have very long to live. Leucotomy, as Scarff has said, offers a relative barrier to pain. With the extension of the disease process and involvement of other areas, the relief experienced during the early post-operative period tends to disappear. Since the relief may last for from six to nine months, however, the cancerous individual may not survive to experience the recurrence of pain to the former extent. It has been noted that patients with such intractable pain are relieved of their suffering, rather than of the pain itself. Suffering, therefore, may be considered the emotional component of a painful disorder. Furthermore, the pain experienced by these subjects is often of low intensity, in spite of the complaints. If one is to judge of the intensity of the pain which the patient suffers, a good test is to bend the fingers of the patient until the pain in the fingers is worse than the pain in the diseased area. Furthermore, pain of high intensity, such as that due to movement of a collapsed vertebral body, is of short duration and elicits an agonized response from the patient, however extensive his leucotomy may have been. Pain of high intensity is truly unbearable and will throw the patient into shock if long continued. With the suffering of the cancerous patient modified, the patient will often rest more adequately and actually gain weight and strength for a while until the malignant process produces the terminal cachexia.

Non-malignant processes that produce considerable suffering, such as causalgia, phantom limb, tabes dorsalis and post-herpetic neuralgia, are less satisfactorily influenced by leucotomy. In order to be effective for long periods, the leucotomy has to be so extensive that the personality of the patient is adversely affected. This has given rise to a reaction against leucotomy in the treatment of painful conditions. The modified operations are not always successful and the radical operations are disastrous. When the surgeon finds himself in this dilemma, he is justified in his hesitancy to perform any leucotomy.

Section of Ophthalmology

President—R. C. DAVENPORT, F.R.C.S.

[*November* 8, 1956]

DISCUSSION ON THE NEURO-OPHTHALMOLOGICAL ASPECTS OF THE CEREBRAL ANGIOMAS

Dr. Helen Dimsdale: The angiomas are now regarded as relatively common intracranial lesions and the importance of their early diagnosis to facilitate surgical treatment has been stressed in a recent paper by Paterson and McKissock (1956), total excision being possible in about one-third of their cases. Although the territory of the middle cerebral artery is the usual situation for vascular malformations, they also commonly occur in the posterior region of the hemisphere where the posterior cerebral circulation is chiefly concerned in their supply. The clinical features of the subtentorial or posterior fossa angiomas which involve the cerebellum and brain-stem have been described by Logue and Monckton (1954), and Paterson (1955) has described the central angiomas which include those invading the mid-brain. Apart from the orbital angiomas which are rare, it is those angiomas occurring in the posterior part of the hemisphere and in the brain-stem which, due to their anatomical location, are prone to present with ophthalmological manifestations.

Their nature is generally accepted as being that of a vascular malformation of congenital origin. Other synonyms used to describe them include arteriovenous malformations, hæmartomas, and perhaps less correctly, arteriovenous and cirsoid aneurysms. Telangiectatic and cavernous forms occur but in this paper the arteriovenous anomalies will be considered.

The superficial angioma is visible as a mass of vessels in the meninges and on the surface of the hemisphere and may be observed in section to penetrate into the brain substance, tapering towards the ventricle. When deeply situated no abnormality is evident on inspection of the meninges and cortex. The lesion consists of abnormally large and tortuous vascular channels which may have the structure of arteries or veins but frequently show an indeterminate histology. Degenerative changes are common in the vessel walls with calcification which may be evident on straight X-ray examination.

The malformation is capable of increase in size by distension of the abnormal vessels, formation of aneurysm dilatations, and—due to the pressure of the arteriovenous shunt—small vascular channels in the neighbourhood enlarge. Episodes of hæmorrhage with clot formation may cause a sudden expansion. The presence of cerebral tissue between the vessels and their adult structure differentiates the angioma from the capillary hæmangioblastoma which is a true tumour, a distinction stressed by Cushing and Bailey (1928) and supported by Professor Russell (1950). The latter is composed of solid masses of angioblastic endothelial cells which form capillary channels, or liquefy, as in the cerebellum, to produce a cyst with a proliferating mural nodule. As a rare phenomenon the hæmangioblastoma may be associated with congenital cysts in the viscera and angiomatosis retinæ, comprising Lindau's syndrome.

The congenitally installed association in Sturge-Weber's syndrome of trigeminal port-wine nævus, buphthalmos and contralateral hemiplegia with focal fits, has an intracranial component of a leptomeningeal venous nævus and underlying cerebral atrophy. Sturge-Weber's syndrome links up with other malformations and dysplasias, including the phakomatoses.

Cerebral arteriovenous malformations may be associated with excessive vascularity of the scalp, minor capillary angiomas of the skin and abnormalities in formation of the retinal vessels described in the Continental literature as cirsoid aneurysms, but such multiple manifestations are uncommon.

Clinical Features

The material for this paper is drawn from a series of 50 patients, for which I am much indebted to my colleagues at the Maida Vale Hospital for Nervous Diseases, and, in particular, to Mr. Valentine Logue for his surgical records.

The sex incidence showed no significant difference, the age of onset of symptoms varied from 6 to 65, with the third and fourth as the commonest decades, the diagnosis being made on an average about a decade later (Table I). The symptomatology of the angiomas has been fully described by Northfield (1940–41), Mackenzie (1953) and Paterson and McKissock (1956). The cardinal symptoms consist of epilepsy, hæmorrhage, subarachnoid or intracerebral, and periodic headache, the relative incidence of the first two symptoms varying in

TABLE I.—AGE OF ONSET OF INITIAL SYMPTOM

Years	No.	Per cent	Years	No.	Per cent
0–10	5	10	41–50	8	16
11–20	8	16	51–60	5	10
21–30	11	22	61–70	1	2
31–40	12	24			

different series. In the present cases epilepsy was the commonest symptom but periodic headache occurred in 26%. In half the cases hæmorrhage was the diagnostic symptom. Progressive focal signs, notably a hemiplegia, are an uncommon mode of onset (Table II).

TABLE II

Initial Symptoms	Number	Percentage
Epilepsy	17	34
Hæmorrhage ..	15	30
Headache	13	26
Focal symptoms ..	3	6
Subjective bruit ..	2	4
Diagnostic Symptom		
Hæmorrhage ..	25	50

TABLE III

Site	Number	Percentage
Hemisphere:		
Posterior (Occipital, Occipito-parietal, Occipito-temporal)	15	30
Middle	16	32
Anterior	9	18
Central	5	10
Orbital	1	2
Posterior fossa ..	4	8

The symptomatology depends in part on anatomical location and the patients under review will be considered from this aspect (Table III).

Posterior hemisphere angiomas.—The hemisphere lesions provided 15 posteriorly situated angiomas, 11 receiving their vascular supply chiefly from the posterior cerebral artery.

The principal symptom of angiomas in this region was periodic migrainous headache, starting in adolescence and early adult life, and present sometimes as long as thirty years before a hæmorrhage or focal signs resulted in the patient being referred to hospital.

Sir Stewart Duke-Elder (1949), quoting Liveing (1873), has classified the manifestations of migraine into four types: (1) Simple hemicranial headache, (2) sick headache, (3) blind headache in which visual phenomena figure largely, and (4) those in which the manifestations indicate a wider involvement of the sensorium. All four types were represented but the commonest manifestation was blind headache associated usually with an angioma supplied by the posterior cerebral artery.

The following patient is an example of migraine as the sole symptom of an angioma:

Case I.—A woman aged 27 complained of recurrent left-sided headaches for the past eight years which were preceded by flickering lights in the right homonymous half-fields. The visual disturbance lasted about twenty minutes and was followed by a severe left-sided headache, frequently of a throbbing character, exacerbated by moving and coughing, and associated with vomiting. On one occasion she experienced a slight patch of dimness in the right side of her fields of vision which persisted for some hours, but then cleared up.

The only abnormality detected on examination was a faint bruit over the left internal carotid artery. Angiography revealed a large angioma in the left occipital region which was supplied by two branches from the posterior cerebral artery (Fig. 1). Operation was decided against as she

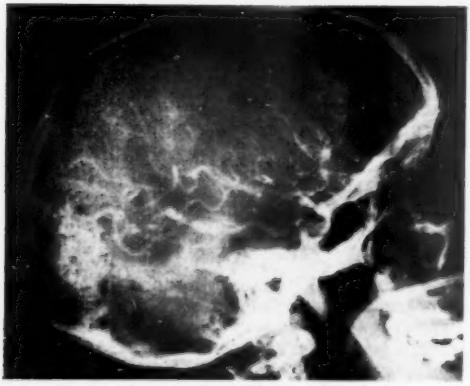


FIG. 1 (*Case I*).—Lateral view of angioma.

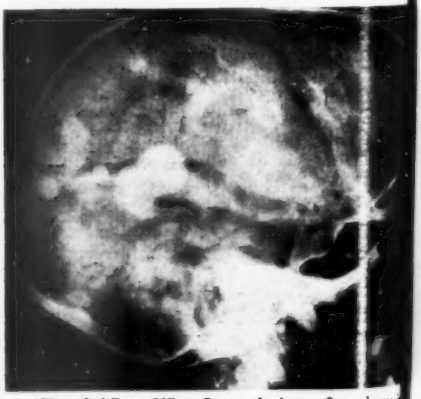


FIG. 2 (*Case III*).—Lateral view of an ioma the venous phase.

had no visual field defect and in addition had experienced no hæmorrhage. The fact that the disturbance always appeared on the same side was perhaps the only point in the history which might have made one suspicious that her migraine was, in fact, symptomatic. Incidentally she has obtained relief with ergotamine tartrate, which is not uncommonly experienced by patients with headaches due to vascular malformation.

Posteriorly situated lesions differ from those elsewhere in the hemisphere in that epilepsy is a less common symptom. Only 4 patients had experienced epileptic attacks which were infrequent and in one restricted to childhood.

Case II.—One patient, a man aged 43, gave the history of a combination of epileptic and migrainous attacks. His fits started at the age of 10, and were preceded by an aura of something passing across his fields of vision from right to left, and objects in his left visual fields appeared "strange". He then experienced left-sided tingling and a noise like a dynamo in his head for half an hour, after which he became unconscious and had a generalized convulsion. At the age of 33 migraine predominated with a left hemianopic onset, and flashing lights synchronous with his heart beat in the blind half-fields, a distinguishing feature from idiopathic migraine in which according to Butler (1941) the rate of flicker in the visual fields is equal to alpha rhythm. Ultimately this patient developed a left lower homonymous quadrantic field defect, and angiography revealed a large right parieto-occipital angioma.

Hæmorrhage was the reason for investigation in 10 patients. Bleeding due to an angioma, particularly if superficially placed, appears less catastrophic than that due to an intracranial aneurysm, and a patient may survive several subarachnoid hæmorrhages.

The usual focal result of a bleed from an angioma in this region is the appearance of a persistent homonymous field defect but in one patient an attention defect resulted. A troublesome feature which may follow on recovery from a subarachnoid hæmorrhage is the development of persistent headache in addition to the periodic exacerbation.

The sudden development of focal signs may occur without evidence of a hæmorrhage and is due perhaps to a sudden dilatation of an angiomatous coil of vessels.

Case III.—An accountant, aged 53, had experienced periodic frontal headaches for twenty years, with photophobia. When adding up his bridge score in a hot room he developed a headache and suddenly found that he was unable to calculate. During the course of the next few days he noticed that he could not see objects on his right side, that he had difficulty in reading and tended to use words incorrectly. He also was troubled by a rushing noise in his head. He showed a right homonymous hemianopia sparing fixation, alexia, and a partial Gerstmann's syndrome consisting of confusion of his right and left, inability to select and recognize individual fingers when looking at both hands, and difficulty in calculation. There was a loud systolic bruit audible on auscultation of the skull in the left mastoid region. Angiography confirmed the presence of an angiomatous malformation with huge venous channels in the left occipito-parietal region supplied by both meningeal and occipital arteries, and by the right vertebral artery (Fig. 2). This mass of vessels had presumably interfered with cerebral function in the region of the left angular gyrus.

Surgical treatment consisted of ligation of the left common carotid and both occipital arteries, and since that time he has been well. The focal signs with the exception of the bruit and field defect cleared. He still has occasional headaches under stress, relieved by phenobarbitone.

Abnormalities of the fundi were not observed except for papillœdema in one patient with focal signs, which persisted after removal of the occipital angioma.

What features in a history of periodic migrainous headache would make one suspect the presence of an angioma? Chiefly the persistent lateralization of the headache to one side, though generalized headache may occur. A family history of migraine or its absence does not assist the diagnosis. Such a history was absent in these cases but Paterson and McKissock (1956) in a larger group, considered that their patients presenting with periodic migrainous headache had a higher family incidence of migraine than a control group. There may also be a history of an episode of acute exacerbation of headache which confined the patient to bed, or even of an attack of "meningitis" followed perhaps by a persistent field defect. A cranial bruit is a valuable sign in adults, frequently audible in the carotid triangle or mastoid region, and occurred in about half the patients with occipital angiomas. Homolateral facial telangiectasis of a minor character was observed in only one patient.

The middle group of hemisphere angiomas which include Sylvian and temporal lesions, usually presented with epileptic attacks or less commonly a hæmorrhage, often intracerebral and producing lesions of the optic radiation.

Case IV.—Intracerebral bleeding into the right temporal lobe in one woman aged 59 produced a homolateral III nerve palsy, possibly due to compression of the nerve against the peduncle, a quadriplegia maximal on the left, and a left homonymous hemianopia. In spite of her grave condition, she made a complete recovery following evacuation of blood and excision of the angioma.

The anterior or fronto-parietal angiomas provided 18% of cases. Headache was not a common complaint but epileptic attacks occurred in every patient except 3 when a hæmorrhage was the first indication of the presence of a vascular abnormality.

Case V.—One patient with a large left frontal-parietal angioma and a right hemiplegia showed a facial spider nævus on the bridge of the nose. He also had a variable proptosis on the side of the lesion which may have been responsible for his complaint of fluctuating diplopia, and a frontal bruit.

The central angiomas have been defined by Paterson (1955) as arteriovenous malformations situated in the thalamus, basal ganglia, internal capsule and mid-brain. The majority of his series of 9 presented with a contralateral hemiplegia of slow or rapid onset and with sensory loss and in some patients a partial or complete homonymous defect. Episodes of hæmorrhage might occur and rarely fits; migrainous headaches were not a symptom. Mid-brain disturbances were observed consisting of weakness of vertical gaze, pupillary abnormalities, nystagmus, external ocular palsies and ptosis.

Similar ocular disturbances with long tract signs were described by Wyburn-Mason (1943) in a series of mid-brain vascular malformations entitled arteriovenous aneurysms, which were unusual in the high incidence of congenital anomalies of the retinal vessels and trigeminal facial nævi.

The central angiomas in the present series showed an incidence of about 10%. There was a marked variation of age of onset of symptoms from 6–43 years of age The usual mode of presentation was a progressive hemiparesis or ataxia of the contralateral limbs. This might be associated with a homonymous hemianopia, presumably due to involvement of the optic radiation, as in one woman aged 21 with a history of left-sided migrainous headache since the age of 16, in whom angiography revealed an angioma situated behind the sella in the left basal ganglia region.

Posterior fossa angiomas.—Both the cerebellar angiomatous malformations described by Logue and Monckton (1954) produced symptoms of an apoplectic onset with headache or confusion, dysarthria, cerebellar signs, and diplopia due to an external rectus paresis with nystagmus in one case.

The brain-stem group, which, unfortunately, are less amenable to treatment than supratentorial lesions, are ophthalmologically interesting because although they may present with a subarachnoid hæmorrhage, in some the onset may be insidious and the picture one of progressive focal symptoms with ocular palsies. The brain-stem angiomas extend along the floor of the third ventricle to the pons and fourth ventricle. The collection of abnormal vessels are inextricably interwoven with the brain-stem and may cause displacement of the aqueduct and 4th ventricle backwards, resulting in internal hydrocephalus.

Signs of III and VI nerve involvement appear combined with other cranial nerve palsies, cerebellar ataxia and long tract signs, which may be unilateral or bilateral and show an intermittent progression for as long as fifteen years.

In those with a long history, disseminated sclerosis requires distinction, and the absence of any story of retrobulbar neuritis is helpful. Headache also is more prominent. Glioma of the pons has a more rapidly progressive course. Myasthenia gravis may be suspected due to the fluctuating course, but the palsies do not respond to neostigmine. A bruit may be audible in the posterior occipital region, and characteristic changes in the X-rays of the skull which have been described by Sutton (1952).

The general circulatory effects of an angioma tend to occur when the lesion is large, with a big arteriovenous shunt which has been present for a number of years. There may be cardiac hypertrophy and an increased pulse pressure. The presence of a free arteriovenous shunt with cerebral atrophy due to ischæmia may produce some degree of dementia.

I have only observed this in one patient, a woman aged 59, with a huge right-sided fronto-parietal angioma, who ultimately developed severe mental changes so that treatment in a mental hospital became necessary.

The history, the presence of a bruit and perhaps cutaneous vascular nævi would suggest the diagnosis of an arteriovenous malformation, and as with a neoplasm the electroencephalogram may indicate a focal abnormality. The essential investigation is angiography, only those lesions in the anterior temporal region occasionally escaping detection.

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Mr. H. E. Hobbs: In the group of arteriovenous malformations which provide the material of this discussion, primary retinal vascular abnormalities appear to be rare unless the site of the intracranial lesion is so close to the eye that the vasculature of the globe is itself involved in the angiomatous process. Increased tortuosity of the retinal vessels has been described with intracranial angiomata remote from the orbit and in Northfield's (1940–41) case, an angiomatous formation close to the disc was seen. No such abnormalities were found in the series to which Dr. H. Dimsdale has referred, nor in those reported by Olivecrona and Riives (1948) or by Logue and Monckton (1954). Mackenzie (1953) and Dandy (1928) each include in their series a single case in which the retinal vessels were grossly distended and tortuous, the veins being virtually indistinguishable from the arteries, and in Paterson and McKissock's (1956) series 2 similar cases are included; but since these arose in conjunction with angiomatous lesions of the orbit or pituitary region, and the changes appear to have been of a secondary nature, I propose to refer to them separately in connexion with the orbital case which Dr. Dimsdale has already mentioned.

That primary vascular abnormalities are occasionally observed with intracranial lesions remote from the orbit, however, is demonstrated by Northfield's case (Northfield, 1940–41).

The main ophthalmological interest of the majority of these cases lies in the characteristic history of migraine, its association with other neurological abnormalities and the evidence of hemianopia when the progress of the lesion has led to a more or less permanent involvement of the visual fibres or cortex. Ipsilateral exophthalmos, which was regarded by Cushing and Bailey (1928) as a change resulting from progressive arterialization of the angioma, has not been seen in this series—possibly because it is a later manifestation of the condition.

With regard to the field changes: these usually follow and may closely resemble the early visual aura and are then commonly of the homonymous hemianopic type; but the defect, while succeeding a hemianopic aura, may occupy only a quadrant of the field, as was seen in a recent case (*vide infra*) which presented to me. It seems likely that these ensuing field defects are not all of them evidence of permanent ischæmic lesions of the visual neurones, but are in some cases the result of compression by an expanding lesion and potentially recoverable if this process is controlled, either spontaneously or by surgical methods. Such recovery is seen in some cases and is illustrated by that of a man (W. H. M.) whose right parietal angioma had, when he was first examined on 21.6.49, produced the incomplete lower left quadrantic hemianopia, shown in Fig. 1.

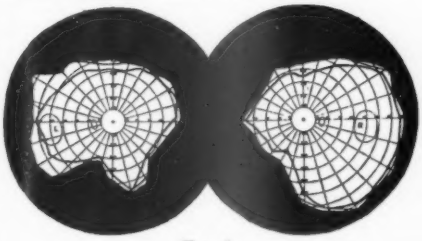


FIG. 1.

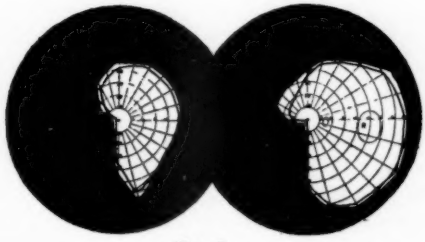


FIG. 2.

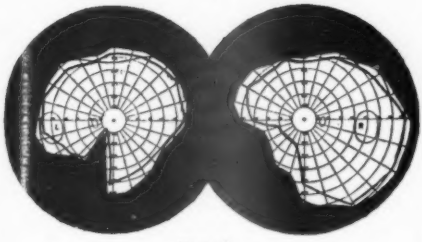


FIG. 3.

Within the next few weeks the defect increased to an almost complete hemianopia (Fig. 2). But following the ligation of the vessels supplying the tumour (Mr. Valentine Logue) a certain amount of recovery of the field was seen (Fig. 3). The importance of the characteristic history has already been emphasized; but as not infrequently happens with disorders of this type, it is the atypical case which appears in the ophthalmologist's consulting room, and the case which I have referred to above was of this type, for her history at first included no reference to migrainous headaches—these had ceased for some years when she presented complaining of bright spots of light in the right eye succeeded by a permanent ?-shaped black spot. She was moderately myopic, the vitreous of the eye in question showed an opacity corresponding to the black spot which she saw, and, after searching unsuccessfully for signs of retinal detachment, I accepted this as the cause of her symptoms with a provisional diagnosis of senile hyalitis. Within a week she had a severe left hemicrania with a hammering sensation in the skull, nausea and prostration followed by blindness on the right side and when I examined her a day or so later a right

inferior quadrantic hemianopia remained. Arteriograms subsequently revealed an angioma involving the left optic radiations. The case is of interest in this connexion, I believe, because of the diagnostic pitfalls which it presents, not only in the long silent interval between the attacks of migraine, but also in the quite unformed character of the spots of light which she saw at the onset of the attack.

Vascular abnormalities which directly affect the eye and orbit form a much smaller group, but one which is also of great interest to the ophthalmic surgeon. One such is included in the present series of cases, and is that of a man (J. H.) who for some years before his admission to Maida Vale Hospital had suffered from recurrent attacks of trigeminal neuralgia which were temporarily relieved by alcohol injections. For many years he had been aware of a cluster of tortuous venules on the temporal side of the sclera of his left eye and four months before I first examined him he had begun to have periodic attacks in which the eye became more congested, first in this region and later over the whole of the eye. The congestion gradually became more constant and proptosis developed whilst at the same time he began to notice a sound synchronous with the pulse, which he described as "squeaking" in his left ear. When I first saw him the proptosis of the left eye was some 7 mm. and chemosis was marked, vision in the eye was reduced to 6/18 and in the fundus gross distension of the retinal veins with œdema and hæmorrhages about the disc were apparent. A bruit, synchronous with the pulse, was audible maximally over the left temple. Arteriography shortly afterwards displayed an arteriovenous communication involving a group of the superior orbital vessels, and at operation a few days later (Mr. Valentine Logue) exposure of the orbital contents displayed a collection of greatly distended veins communicating with the ophthalmic artery. Ligation of these vessels effected a prompt cessation of the bruit and the proptosis very shortly subsided, with improvement in vision and restoration of the normal fundus appearance so that when I examined him a few weeks ago visual acuity was 6/9, the field full and the eye white, with the exception of the collection of varicose episcleral veins. The appearance of the fundus at this time was quite normal, without venous distension and with no suggestion of abnormal retinal vessels.

In this instance, therefore, although the proptosis and retinal changes arose from the presence of an arteriovenous malformation of the orbit they were evidently reversible and secondary to the arterialization of the retinal veins to which it gave rise. The mechanism is one which is common with such angiomata and examples of similar vascular lesions have been reported by Paterson and McKissock and by Mackenzie, whilst in Dandy's (1928) Case 12 a lesion in the pituitary region was responsible. It is probable, however, from the description which Cushing and Bailey give of their Cases 9, 11 and 14 in which arterialization of the retinal veins was seen with temporal and occipital angiomata, that similar changes may be seen with more remote lesions when circulatory changes become more widespread.

In such cases it is evident from the operative and arteriographic findings that the vascular abnormality has a more simple character than is the case with angiomata involving, say, the cerebral cortex where the collection of vessels may form a more or less circumscribed mass. Their essentially arteriovenous nature is the more obvious for this reason, and they tend clinically to bear some resemblance to carotico-cavernous fistulæ; but the insidious onset, absent or minimal pulsation of the eye and absence of trauma in the history are distinguishing features. In our case, however, the conspicuous collection of abnormal episcleral vessels provides a further indication of the presence of a primary vascular abnormality.

In contrast with such secondary retinal changes are those of the group in which the retina shows primary vascular abnormalities associated with retro-ocular angiomatous formations, the extent of which varies widely. It may be limited to the orbit and pituitary region or extend along the visual tracts as far as the mid-brain and even, as in one published instance, into the occipital lobe. The retinal picture varies in these cases and simple arteriovenous communications, enlarged and tortuous vessels which in some cases are abnormally numerous, have been described. Circumscribed angiomata and secondary retinal changes are sometimes seen; but retinal detachment has not been reported although Northfield refers to the occurrence of glaucoma in two instances. Optic atrophy has been noted several times and papillœdema is seen as a secondary change with raised intracranial pressure.

An angiomatous appearance of the retina was recorded in a case (No. 3) described by Brock and Dyke (1932). The eye was blind and proptosed and the neurological abnormalities present arose from the angioma which was seen at post-mortem to extend from the eye along the optic nerve and tract to the mid-brain and thence into the cerebellum. The case is of especial ophthalmological interest since the histological appearances of the eye were subsequently reported on by Krug and Samuels (1932) who verified the changes as those of a venous angioma. Retinal changes of this type were seen also by Olivecrona and Riives (1948) in a patient with a lesion extending to the mid-brain. In Yates and Paine's (1930) case in which the ocular signs consisted of homonymous hemianopia and slight proptosis, the retina showed only slight dilatation of the vessels; but with a collection of aneurysms at the periphery. Professor Bonnet of Lyons (Bonnet *et al.*, 1937) also reported a case in

which hemiplegia, ocular palsies and exophthalmos with an audible bruit over the affected eye occurred with the angiomatous appearance of the retina.

These extensive angiomatous formations were the subject of an interesting review by Wyburn-Mason (1943) and his paper contains a collection of fundus pictures drawn from many sources which demonstrates the considerable variation in the vascular anomalies met with in this connexion. His own Case 7 is of especial interest since the sole retinal abnormality which accompanied the intracranial lesion was a single arteriovenous aneurysm.

Optic atrophy has been apparent in association with other defects in several of the published cases; but that it may present as the sole neurological sign is shown by the case reported in 1952 by Band from the United States. Here the angioma demonstrated by angiography and operation surrounded the chiasma and one optic nerve. The case may be correlated with that of the man (W. J.) with cutaneous angiomata, postural proptosis and a spastic limb (shown at the Meeting). The angioma in this instance has been shown by angiography to extend from the orbit upward toward the basal ganglia and, although the retinal vascular changes are not marked, the suggestion of atrophy at the disc is confirmed by the visual field defect (Fig. 4).

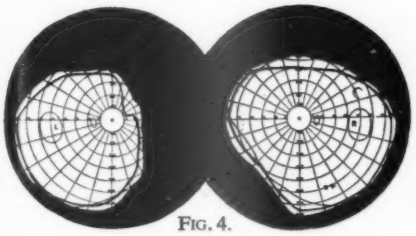


FIG. 4.

The possibility of such an explanation of optic atrophy is clearly, therefore, one to be borne in mind. How far arteriography can be expected to assist in displaying the nature and extent of the lesion in such cases is a matter which Dr. David Sutton will discuss.

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Dr. David Sutton (St. Mary's Hospital, London, and Maida Vale Hospital for Nervous Diseases): *Radiology of Cerebral Angiomas* [*Summary*][1]

Cerebral arteriography has proved the most important means of investigation in the diagnosis of cerebral angiomas and is largely responsible for the elucidation of the clinical pictures presented by them. These lesions were considered rare until quite recently. Cushing's monograph (Cushing and Bailey, 1928) based on a vast experience of neurosurgery, was able to cite only 15 cases. In recent papers Mackenzie (1953) was able to quote 50 cases, and Paterson and McKissock (1956) quote 110 cases. The writer has personally performed arteriograms on over 100 cases in the last ten years. At Maida Vale Hospital 60 cases of angiomatous malformation have been diagnosed by arteriography in the last six years. This is entirely due to the routine use of cerebral arteriography. However, plain X-rays may also be most helpful.

Abnormalities seen on plain X-rays.—These are seen in a relatively small proportion of cases but can be diagnostic. They consist of: (1) Abnormal vascular channels in the skull vault, in particular hypertrophied and tortuous meningeal vascular channels. These must be differentiated from the similar changes seen sometimes with meningiomas. (2) Calcification. This has been recorded in 10% to 24% of cases in different series. In my own series it was present in 16 cases or 14%. The calcification is often pathognomonic, and in typical cases consists of scattered linear flecks of calcium in the area of the angioma, of a type quite unlike that seen with neoplasms and other intracranial lesions. Sometimes associated annular shadows are seen similar to those described with intracranial aneurysms, These lie in the walls of aneurysmal dilatations in the malformations.

Angiography.—The investigations required depend both on the site and the size of the lesion. In many cases bilateral carotid arteriograms will be required; in others vertebral arteriography will be necessary, sometimes in combination with unilateral or even bilateral carotid arteriography to reveal the total extent of a large angioma and all its vessels of supply

[1]This paper with illustrations is being reproduced in full in *J. Fac. Radiol.*

and drainage. Angiomatous malformations have been called "parasites" or "sponges" in the way they suck blood from all sources of supply. This can be well demonstrated by the arteriograms. The vessels leading to the angioma are hypertrophied, vessels not supplying it are often hypoplastic or fail to fill. Frequently arteriography of the contralateral carotid artery shows blood being sucked across the mid-line to feed the angioma.

Most angiomas show abnormal large veins draining the lesion. These can reach gigantic size. Arteriography shows that they opacify early because of the arteriovenous shunt. Many of the lesions we have considered in this discussion are supplied by the posterior cerebral artery, and it is common for these to be filled equally by the carotid and vertebral arteries. Smaller angiomas occur which can only be demonstrated from one major feeding artery. With tiny and less typical angiomas visualization of a dilated vein in the arterial phase of the arteriogram may be the feature most suggestive of angioma. Such lesions frequently manifest by subarachnoid hæmorrhage or by rupture into the brain with the formation of a cerebral hæmatoma. In this case clotting may occur in the lesion and the tiny angioma may become extremely difficult to identify at arteriography.

Pneumography.—Usually normal appearances are seen, but abnormalities may be seen in three types of case:

(1) Giant angiomatous malformations. These may show the same types of deformity of the ventricular system as those presented by any intracerebral expanding lesion.

(2) Smaller angiomas adjacent to and protruding into the ventricles.

(3) Angiomas complicated by intracerebral hæmorrhage, in which the hæmatoma acts as an intracerebral expanding lesion to deform the ventricular system.

The clinical aspects which concern the ophthalmologist have been described by my colleagues. The most important mode of presentation to the ophthalmologist appears to be *periodic migrainous headache with a visual aura* of the type described, i.e. constant and homonymous in nature. Such symptoms were present in 10 of my cases. *Homonymous field defects* were present in 6 cases. In this group the angioma lay in the occipital, parieto-occipital or temporo-occipital regions. Field defects were sometimes seen with large temporal or para-sellar angiomas. *Papillœdema* was rare but was present in a few cases, usually with excessively large angiomas or following intracerebral hæmorrhage.

Pulsating exophthalmos occurred in one case. *Defects of ocular movement of central type* were seen in 4 or 5 cases, though they were not the presenting or most prominent sign. They were most common with angiomas in the region of the mid-brain.

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The President said that in the course of his research, Mr. Hobbs had come across the notes of a young man whom he, the President, had seen recently. He had had a convergent squint in the left eye since the age of 21 months, and the vision from the eye had always been "very weak". Since the age of 14 he had had visual disturbance, and visible retinal changes in the right eye. These had recently extended. On examination the squinting eye showed so-called primary optic atrophy, with no evidence of previous œdema of the nerve head. The right fundus showed in the upper nasal region a large cystic detachment of the retina, with diffuse tortuosity of all blood vessels in that quadrant. There were smaller areas of detachment in the temporal and upper temporal regions, which in a few months became confluent with the nasal "cyst". The vascular picture in the one eye, and the unexplained optic atrophy in the other, suggested that the next move might be to get Dr. Sutton to undertake arteriography, as straight X-ray of the skull had revealed no abnormalities, and the retinal condition was quite atypical of hæmangioblastoma.

Mr. E. F. King referred to a case of his own, a man of middle age who had been attending his clinic for a number of years. In the upright position both eyes of this patient were enophthalmic, but when he leant forward, or when pressure was applied to the vessels at the root of the neck, the eyes temporarily became prominent. Another interesting feature was that this patient had advanced bilateral simple glaucoma and was, in fact, now blind. He had always assumed that there must be some congenital malformation in the drainage channels of the eye itself, and he wondered if such an association with orbital angiomata had been noted by others.

Another case was that of a child. Last year, when she was a few months old, she developed proptosis. A retro-ocular tumour had been diagnosed and radiation to the orbit initiated. A further examination showed, in addition to the proptosis, a cluster of dilated veins in the temporal region on the same side as the affected eye. It seemed probable that the child had an orbital angioma and that the proptosis, which appeared rapidly, was due to a hæmorrhage from it. All treatment was stopped and the proptosis subsided completely within a few months.

Section of Radiology

President—Professor R. McWHIRTER, F.R.C.S.Ed., F.F.R., Hon. F.C.R.A., F.R.S.Ed.

[*October* 19, 1956]

The Radiological Diagnosis of Pulmonary Embolism

By SHIRLEY ROBERTS, M.B., B.S., M.C.R.A.

Radiodiagnostic Department, Royal Infirmary, Bristol

THE clinical picture presented by a typical case of pulmonary embolism is well defined and characteristic. By contrast, the radiological diagnosis is often uncertain, and the clinician, as a result, may regard chest radiography in suspected pulmonary embolism as either unnecessary or valueless. Further observation tends to show, however, that this is not a true representation of either the clinical or radiological aspects of pulmonary embolism.

PATHOLOGICAL FINDINGS

The inconsistency of both the clinical and radiological features is a reflection of the variety of the pathological changes which may occur and these are related to the anatomy of the pulmonary vasculature. The branches of the pulmonary artery correspond in their distribution to the subdivisions of the bronchial tree, there being no significant anastomoses between the branches to neighbouring segments or subsegments. However, there are important pre-capillary anastomoses between the bronchial and pulmonary arteries. Probably they are normally contracted, but in a number of pathological states become patent.

Hence, although occlusion of a branch of the pulmonary artery produces potential ischæmia of the whole of the segment or subsegment it supplies, the actual extent and severity of the change produced depends largely on the adequacy of the broncho-pulmonary anastomoses.

There is thus a range of possible parenchymal changes:

(*a*) Minimal ischæmia, without significant effect on the parenchyma; (*b*) incomplete infarction, with early return to a normal appearance; (*c*) production of a hæmorrhagic infarct, with ultimate replacement fibrosis.

Infarction may be delayed in onset, due to spreading thrombosis or repeated embolic episodes.

RADIOLOGICAL APPEARANCES

These reflect the complex nature and course of the pathological changes. Four elements compose the radiological picture; (*a*) Changes in the pulmonary parenchyma. (*b*) A pleural reaction. (*c*) Alterations in the diaphragmatic contours. (*d*) Changes in the vascular pattern.

(*a*) *The parenchymal lesion.*—(i) *Site:* A whole lung, lobe or segment may be involved, or the lesion may be subsegmental. However, it always involves a pleural surface and is often at the junction of two pleural surfaces, e.g. costophrenic angle. This peripheral situation is probably due to the fact that ischæmia is maximal in the most distal portion of the field supplied by the occluded vessel. (An analogous phenomenon occurs when some peripheral arteries are occluded; obstruction of the popliteal artery frequently results in gangrene of the toes only.) Approximately 75% of infarcts occur in the lower lobes and they are slightly more common on the right side than on the left. They are frequently multiple, but an upper lobe is rarely involved unless there are also lower lobe lesions.

(ii) *Shape:* The infarct shadow has not, as was once thought, a typical shape. Since it corresponds to a segment, or a peripheral portion of a segment, its shape depends on the projection in which it is viewed. Thus, while it may be wedge-shaped, with its apex pointing towards the hilum, it has more commonly a rounded or "humped" cardiac border with its longest edge applied to a pleural surface (Fig. 1A, B). An infarct occurring in a costophrenic angle has a characteristically convex superomedial margin which enables it to be distinguished from a small effusion (Fig. 2).

(iii) *Density:* The density of the opacity depends on the stage of the lesion. In the early

phase, when there is passive congestion of the alveoli, while the alveolar ducts and atria are still aerated, the parenchymal lesion is represented by a poorly defined area of vague clouding. In cases of incomplete infarction this may be the maximal abnormality observed, serial films showing complete resolution of the opacity within a few days. When the lesion progresses to complete alveolar necrosis, the opacity remains homogeneous but becomes considerably denser and more clearly defined.

(iv) *Time of appearance and duration:* The interval between the onset of clinical signs and symptoms of embolism and the appearance of a parenchymal density in serial films is very variable. Not uncommonly, films taken within the first twenty-four hours fail to show any abnormality, but on the second or third day a large infarct shadow may be apparent (Fig. 3).

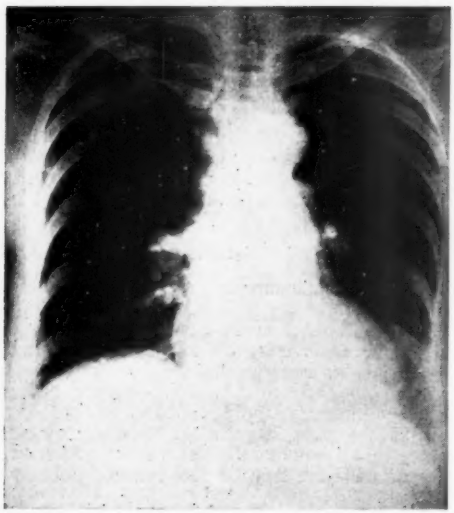


FIG. 1A.—A vague left lower zone opacity is apparent in the P.A. view.



FIG. 1B.—In the left anterior oblique view it is seen to consist of a well-defined parenchymal density with a small pleural effusion.



FIG. 2.—A costophrenic angle infarct with characteristically rounded supero-medial margin.

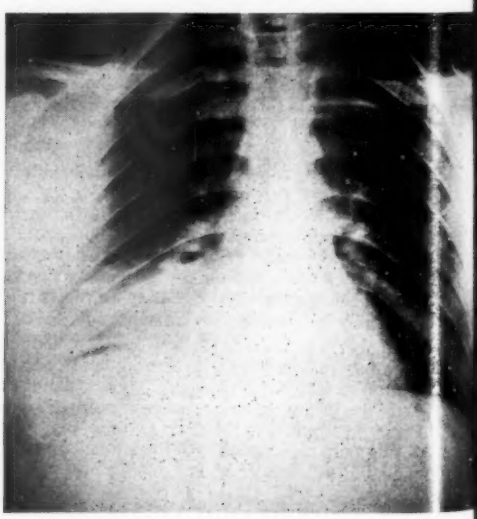


FIG. 3.—Post-operative infarction. Twenty-four hours after the onset of right basal infarction. A film at five hours had shown no abnormality.

On the other hand, a lesion detectable early in the course of the illness may, if due to incomplete infarction, resolve rapidly, so that there may be no radiological evidence of its occurrence a few days later. Hence, repeated examinations at short intervals may be necessary to demonstrate the infarct. Such repeated examinations may also reveal extension of the lesion due to spreading thrombosis.

(v) *Resolution and healing.*—The rate of the healing process in hæmorrhagic infarction depends on the size of the lesion and on the efficiency of the pulmonary circulation. As the mass of necrotic tissue is absorbed and replaced by connective tissue, the lesion decreases in size. Serial films thus show, usually from the second week onwards, progressive shrinkage of the infarct density. If the lesion has been extensive, radiological evidence of loss of pulmonary substance—displacement of interlobar fissures—will also appear at this stage, although not evident earlier.

Most commonly, a small fibrous scar, not detectable radiologically, represents the stage of complete healing. However, larger infarcts may result in a permanent network of irregular linear shadows due to bands of scar tissue. There is often localized pleural thickening overlying these lesions (Fig. 4).



FIG. 4.—Linear scars remaining after a left lower infarct which occurred seven months previously.

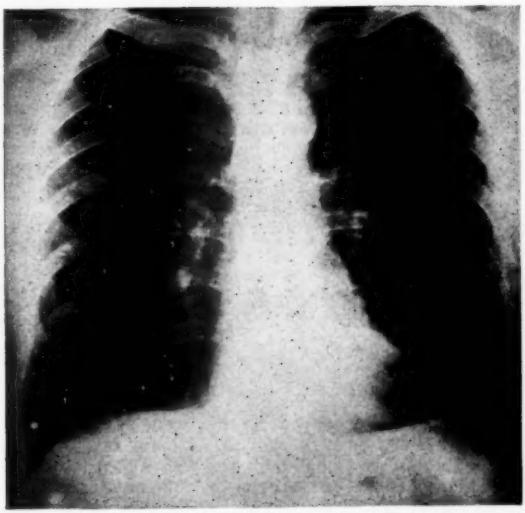


FIG. 5.—Transient irregularity of the left diaphragmatic contour, the only radiological sign observed in this case of left basal pulmonary embolism.

Occasionally an infarct is too large to permit of complete fibrous replacement and the hæmorrhagic centre persists indefinitely. The associated radiological abnormality—a parenchymal shadow devoid of characteristic features—may present diagnositic difficulties if encountered for the first time long after the embolic episode.

(*b*) *The pleural reaction.*—A pleural reaction, detectable radiologically, is present in less than half the cases. Moberg (1948) investigated the incidence of effusion within the first three days of illness in a series of cases of pulmonary embolism, as compared with bronchopneumonia of the same duration. He found that, in 21 of his 46 cases (i.e. 45%) of embolism, an effusion was the dominant radiological feature, overshadowing the parenchysmal density. In only 2 of the 23 cases (9%) of bronchopneumonia was an effusion, rather than a parenchymal density, the major radiological abnormality.

The extent of the effusion in cases of embolism varies from a thin layer, detectable perhaps in only one projection, to massive collections obscuring most of the underlying lung. Small effusions are sometimes detectable in P.A. or A.P. films taken with the patient lying on the affected side and using the horizontal beam, but the standard oblique projections are also helpful (Fig. 1). Localized pleural thickening may remain to indicate the site of an old infarct.

(*c*) *Changes in the diaphragmatic contours.*—Short (1951) found elevation of the diaphragm in 35% of cases. Occasionally it is the only radiological abnormality in cases where the

clinical diagnosis is definite (Fig. 5). Transient elevation of the diaphragm on the side of the lesion may be noticed in the first few days of the illness. In other cases it appears, and persists, when healing of the lesion is associated with a decrease in lung volume.

(*d*) *Changes in the vascular pattern.*—A different sign, of considerable radiological interest, is that described by Westermark (1938). This consists of the appearance of an area of reduced vascularity, apparently due to spasm of the vessels distal to the occlusion. The only vascular markings visible within the ischæmic zone are those of the bronchial vessels. This appearance may persist for a number of hours and then be replaced by a return of the normal vascular pattern, or by the appearance of an infarct shadow. Enlargement of the area of ischæmia indicates spreading thrombosis and is of serious prognostic significance.

Conclusion

There is no commonly found radiological appearance which is completely characteristic of pulmonary embolism. However, there is a group of signs which, in their relation to each other and to the clinical picture, constitute a pattern which can be recognized as being due to embolism rather than to the various conditions resembling it.

Many cases of pulmonary embolism cannot be diagnosed on clinical evidence alone. Even in very ill patients, radiography of the chest with portable apparatus causes minimal disturbance and there is ample justification for using this diagnostic aid.

Acknowledgments

The author is indebted to Dr. J. H. Middlemiss for his advice and encouragement and to Dr. F. G. M. Ross and Dr. I. R. S. Gordon for their helpful criticism.

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Radiological Manifestations of Ectopic Salivary Adenomas showing the Cylindroma Pattern

By Max J. Ryan, D.M.R.D.

Senior Registrar, Manchester Royal Infirmary and Christie Hospital and Holt Radium Institute

This short paper describes some of the interesting features of a rare tumour which is found in and around the mouth. Locally it grows slowly but travels extensively, with a tendency, in some cases, to invade the base of the skull. Its most striking characteristic is the production of pulmonary metastases which show little increase in size or number over a long interval of time.

The benign mixed salivary adenoma is one of the commonest adenomatous tumours found in the anterior foregut. It usually arises in one of the large serous salivary glands—namely the parotid or submandibular—and its course is usually benign. Rarely, however, adenomatous tumours are discovered outside the large salivary glands, for example, in the hard palate, the soft palate, the tongue, the antra and the post-nasal space. Rightly or wrongly, these tumours are described as arising in ectopic sites.

In the Christie Hospital it has been found that many of these tumours arising in an ectopic site have recurred after treatment of what was originally considered to be a benign mixed salivary adenoma. Some of these tumours even gave rise to regional and distant metastases.

As a result, it was decided to review all the histological material of the adenomas arising in ectopic sites between the years 1937 and 1952. A total of 82 was found, which Russell (1955) has classified as follows:

Cylindromas, 46; Mixed adenomas, 29; Other adenomas, 7.

The Cylindroma

Russell has described the cylindroma as a specific variety of the mixed salivary adenoma. It is essentially an adenoid structure which appears to arise from the mucous glands, which are most common in the buccal cavity and upper respiratory tract. The cylindroma has quite a distinct pattern, a special stain showing successive zones or cylinders of cells, which gave rise to the term cylindroma. It is incompletely encapsulated and grows slowly. Initially bone erosion is caused by extrinsic pressure rather than malignant invasion. Harrison (1956) in his Hunterian lecture has reported on the clinical behaviour, treatment and prognosis in this same series of cases.

The material which I have studied is this group of 46 cases reported by Harrison (1956) and Russell (1955), and some 9 others which have since been added, making a total of 55 cases in all. Of these 55 cases, radiological investigations were carried out in 32, and X-ray changes were found in 24. All the cases were not submitted to X-ray examination—for example, when the primary was situated in the tongue, floor of mouth and fauces. There were 6 cases of metastases to lung and 2 to bone.

Radiological manifestations of the cylindroma have been found in the nasopharynx, the antrum, the hard palate and the orbit. The following is the incidence in each site:

Nasopharynx, 8; Antrum, 6; Hard palate, 8; Orbit, 2.

My first case shows how the cylindroma may behave in the post-nasal space.

A man aged 42 presented with a history of recurrent attacks of pain on the left side of the hard palate for *eight* years. On examination he was found to have a lesion of the left trigeminal nerve.

X-ray examination of the skull showed enlargement of the left foramen ovale.

On exploration of the left middle cranial fossa a "berry-like" tumour was seen protruding from the left foramen ovale and foramen spinosum. The tumour was completely extradural and was infiltrating the left trigeminal nerve. On histological examination it was found to be a cylindroma.

The involvement of the trigeminal nerve appears to be a characteristic feature of many tumours found in this region as described by Sir Geoffrey Jefferson in his Bowman Lecture of 1953.

Further X-ray investigation after the operation and review of the previous films revealed the following features. On the basal view (Fig. 1), in addition to the enlarged left foramen ovale, there was opacity of the left sphenoidal sinus, left nasal cavity and possibly the left antrum.

A lateral view of the neck disclosed definite evidence of a nasopharyngeal tumour (Fig. 2).



FIG. 1.—Basal view of skull showing enlargement of the left foramen ovale and opacity of the left sphenoidal sinus and left nasal fossa.



FIG. 2.—Tumour in post-nasal space.

The occipito-mental view showed opacity of the left antrum.

There was also loss of translucency in the ethmoidal air cells and enlargement of the left sphenoidal fissure.

On tomography of the antra and ethmoidal sinuses the tumour was found to have eroded the floor and the medial wall of the left orbit. The tomograms also demonstrated destruction of the turbinates of the left nasal cavity and thinning of the medial wall of the left antrum.

On follow-up examination fifteen months later there was involvement of the right antrum in addition to the left, but there was no further intracranial extension. It is remarkable that in spite of all these changes the patient continues to enjoy moderately good health.

This case illustrates that when a cylindroma is proved or suspected, an extensive radiological examination is essential to reveal all the extensions of the tumour.

The antrum was the site of origin in 6 cases, all of which showed radiological changes.

The next case illustrates the progress of a cylindroma of the antrum over five years.

Radiologically this man of 41 presented with a tumour of the right antrum, which was destroying the floor of the orbit and invading the nasal fossa (Fig. 3A). It will be seen that there was no evidence of involvement of the left antrum. He was treated by radical excision of the right maxilla and insertion of a radium tube.

Three years later he complained of a bulging right eye. X-ray examination revealed the presence of extensive and widespread tumour recurrence (Fig. 3B). There was tumour in the right nasal cavity and extension across the nose into the left antrum. The well-defined opacity in the right infra-orbital region was due to the operative defect. Recurrence was also found in the right ethmoidal region with thinning of the floor of the anterior fossa. Subsequent operation confirmed the X-ray findings. Tumour recurrence was present in all areas.

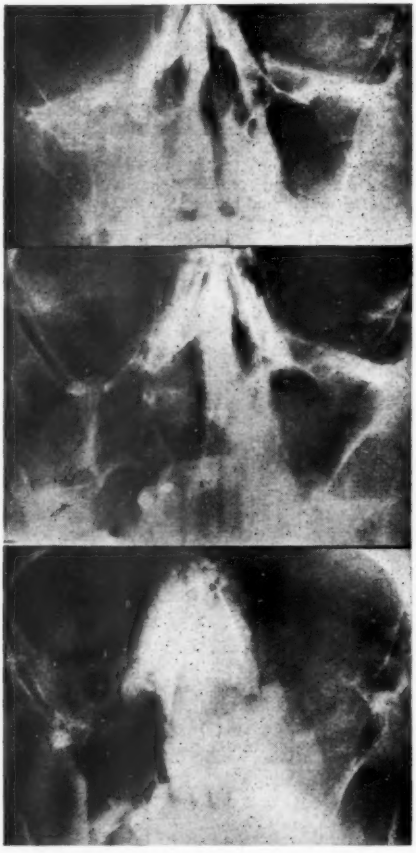


FIG. 3A.—Antral tumour destroying the floor of the right orbit and invading the nasal fossa.

FIG. 3B.—Three years later—tumour recurrency in right nasal cavity with extension across the nose into the left antrum.

FIG. 3C.—Two years later—left maxillary sinus completely filled with tumour which has destroyed the floor of the left orbit, and the medial wall of the antrum.

After another two years he began to complain of protrusion of the *left* eye. Radiological examination showed that the left maxillary sinus was now fully occupied by the tumour, which had completely destroyed the floor of the orbit and the medial wall of the antrum (Fig. 3C). The nasal cavities and ethmoidal sinuses were packed with the growth, and there was erosion of the greater and lesser wings of both sphenoid bones.

Despite this long course and the presence of extensive destruction, the general condition of the patient is reasonably good.

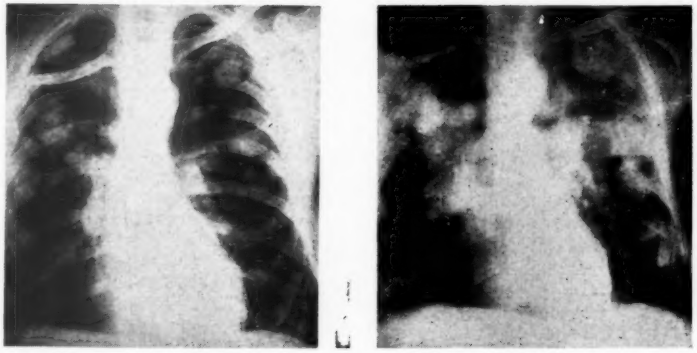
The hard palate is the commonest site for the cylindroma to be found clinically, but only a small number show X-ray changes. Radiologically the hard palate tumour often simulates a malignant antrum. Sometimes in an advanced case it is impossible to differentiate between the two.

The next case is an example of a cylindroma which first presented as an orbital tumour.

A man of 47 gave a two-year history of pain behind the left eye, and more recently proptosis and diplopia. Radiological examination of the skull showed some loss of definition of the margins of the greater and lesser wings of the left sphenoid (Fig. 4).



FIG. 4.—Erosion of the greater and lesser wings of the left sphenoid bone.



A B

FIG. 5.—Multiple round cannon-ball metastases—six-year interval between films A and B.

At operation a tumour was found behind the left orbit and in the left pterygoid region, which was invading the temporal fossa.

METASTASES

A surprising feature of the cylindroma is its tendency to produce pulmonary metastases. Here we have a relatively innocent tumour, which invades locally but grows very slowly over the years, and yet we have *six* cases of metastases in the lungs. The amazing characteristic of these cylindroma metastases is that they grow very slowly, like the primary, and the patient is free from symptoms.

Fig. 5A was a routine chest X-ray taken in 1950, eight years after treatment of a cylindroma of the antrum. The patient, a male nurse, had no reason whatsoever to suspect that he had any chest disease. The prognosis given at that time was, of course, extremely poor—at the most six to nine months. Since then chest X-rays have been taken at regular intervals and Fig. 5B was taken three weeks ago. It is remarkable that there has only been a moderate increase in the size and number of the metastases over six years and even stranger is the fact that the patient is well and has had no recurrence of his primary.

CONCLUSION

The cylindroma is notoriously difficult to diagnose, both clinically and radiologically. The changes due to the primary tumour can be produced by many other lesions. The diagnosis is essentially a pathological one, and may give rise to considerable difficulty.

When the cylindroma has been diagnosed, radiology can make a definite contribution by disclosing all the extensions of the tumour which may not be suspected clinically.

A chest X-ray must not be omitted, for the finding of round well-defined metastases in the lungs, which show very little change over a long interval, enables the radiologist to make a fairly confident diagnosis.

ACKNOWLEDGMENTS

I wish to express my sincere thanks to Dr. E. Duff Gray and Dr. J. Blair Hartley for their constant encouragement and advice, to Mr. Kenneth Harrison, Mr. R. T. Johnson, Dr. Ralston Paterson, Mr. W. F. Nicholson, and Dr. Helen Russell for permission to publish cases and to Dr. R. G. W. Ollerenshaw and his staff of The Department of Medical Illustration for the excellent prints.

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Bone Changes in Myelosclerosis

By F. MULCAHY, M.B., B.Ch., D.M.R.D.

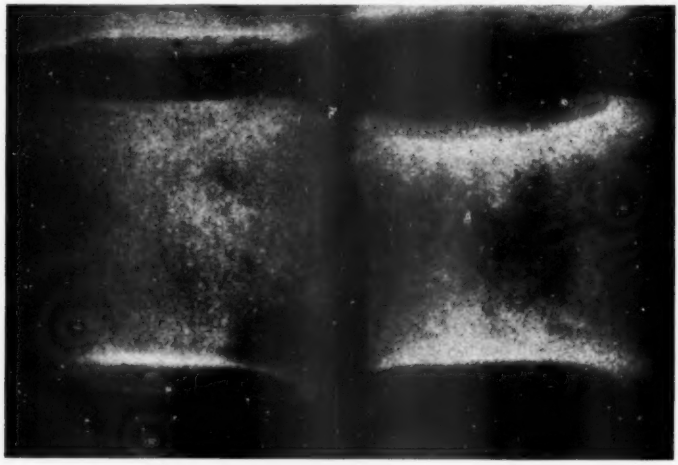
Department of Diagnostic Radiology, Manchester Royal Infirmary

MYELOSCLEROSIS is a rare disease of unknown ætiology occurring in later life and characterized by leuco-erythroblastic anæmia, progressive splenomegaly, obliteration of the normal bone-marrow by fibrous tissue and frequently by cancellous bone. Many cases appear to have been described under various other titles such as Myelofibrosis, Osteosclerosis, Osteomyelo-reticulosis, Aleukæmic Ossifying Myelosis and Megakaryocytic Leukæmia. Some writers refer to primary and secondary myelosclerosis. I shall describe the primary or idiopathic form. The secondary type refers to the sclerosis which occurs in bone as a result of other conditions, such as Generalized Osteoblastic Carcinoma; Osteitis Deformans; Hodgkin's Disease; Syphilis and Post-radiation Sclerosis.

The present study is based on a detailed investigation of 28 cases of the disease by Leonard *et al.*, in the Manchester Royal Infirmary. I propose to summarize the findings and correlate the radiological appearances with these.

The sex distribution of cases was equal in the series. The onset of the disease was insidious and was frequently unnoticed until it was well established. The majority of patients were over 45 years and presented with symptoms of:

I. Anæmia, such as dyspnœa, tiredness and angina pectoris.
II. Splenomegaly, such as a heavy feeling in the abdomen or distension after meals.
III. Bone involvement, such as deep-seated pain in the shoulder or hip-joint regions and occasionally over the shafts of long bones.



A B

FIG. 1.—A, Normal vertebral body. B, Myelosclerotic vertebral body showing alteration in trabecular pattern, with increased density close to the cartilaginous plates.

It is interesting to note that the patients who complained of bone pain showed well-marked radiological bone changes.

[Dr. Mulcahy then reviewed the changes seen in the peripheral blood and bone-marrow and stated that sternal marrow aspiration was impossible in 50% of cases. He showed several photomicrographs of bone-marrow taken from biopsy specimens and pointed out that the quantity of new bone deposited upon the trabeculæ varied considerably from case to case, observing that the degree of change noted on the bone films was related to this.]

I have examined the skeletal survey films of 19 cases where the diagnosis was confirmed by bone biopsy. In 10 there were no detectable abnormalities. 9 showed X-ray changes of varying degrees. Of these, 4 were abnormal on casual inspection. The remaining 5 showed definite but less well-marked changes.

The bones most frequently involved are those of the central skeleton. The changes are less conspicuous towards the periphery. The bones distal to the elbow-joint are normal in all cases and I have only seen bone involvement below the knee-joint once.[1] No skull changes are present in any of the cases. These findings agree with those of other observers.

Some difficulty may be experienced in detecting the earlier changes, but Brailsford (1953) pointed out that the alterations are easier to appreciate if the films are examined with those



A B

FIG. 2.—A, Myelosclerotic bone showing granular density and loss of trabecular pattern. B, Normal ischium and pubis.

of similar areas in normal cases. I have found this valuable, but there is such variation in the structure and architecture of normal bones that I have used several control films for each site because of difference in sex, age and bone size.

In some cases the earliest detectable changes consist of a widening and increased prominence of trabeculation against a background of slightly increased density. Other cases show patchy ill-defined areas of sclerosis, an appearance which may occasionally be mistaken for metastatic deposits. Others show larger areas of generalized amorphous or granular increase in density in which the spongiosa architecture cannot be identified. This appearance is usually found in the ischium pubis and ribs, where trabeculation is normally fine.

In more advanced cases, the ordered well-defined medullary pattern is replaced by coarse irregular trabeculæ which have ill-defined edges. The inner margin of the cortex is sometimes uneven and poorly differentiated from the medulla.

Vaughan and Harrison (1939) have described, in addition to other changes, a marked decreased density of cortical bone together with subperiosteal new bone formation. I believe their cases were more advanced than those which I have reviewed. The longest observed

[1] ADDENDUM.—Since this paper was delivered I have seen two advanced cases of myelosclerosis in which the bone changes extended as far as the wrist and ankle joints. In addition, one of them showed a small periosteal reaction at the lower end of the femur.

case in the present series was first seen four years ago and the patient is still alive. I have not noted any periosteal new bone formation or accentuation of muscular insertion sites.

The following are some examples of the abnormalities found. The pelvic bones of a man of 65 years, who complained of weakness, dypsnœa and anorexia for two years show a generalized increase in density. Patchy areas of sclerosis are present in both ilia and in the upper femora, where trabeculation is coarse. Closer examination of the ischium and pubis, together with a normal control, reveals an amorphous increase in density with obliteration of the trabecular pattern. A generalized density affects all the ribs, the individual trabeculæ being ill-defined. In the lower aspects of the scapulæ areas of sclerosis are present. The dorsal spine, in addition to some generalized increase in density, shows small central sclerotic areas. Patches of sclerosis and trabecular alteration are present in the upper humeri.

A woman of 61 years complained of symptoms of anæmia and discomfort, due to splenic enlargement, for two years prior to examination. In the pelvic bones, widening and coarsening of trabeculation are present and the enlarged splenic shadow is visible on the film. When compared with a normal control the trabecular alteration is more striking, especially in the femoral heads.



FIG. 3.—Femoral neck showing increased prominence of the weight-bearing trabeculæ.



FIG. 4. — Upper humerus. Note trabecular alteration, hazy sclerosis and ill-defined areas of porosis.

The next patient, a woman of 48 years complained of symptoms, due to anæmia and splenomegaly, for only two months before her X-ray examination. The bone texture of the vertebral bodies is obviously abnormal. Trabeculation is coarse and ill-defined, but the increased density is a little more marked close to the cartilaginous plates, giving a "sandwich effect". Fig. 1B shows this appearance in one of the vertebral bodies, together with a normal control (Fig. 1A). Schinz *et al.*, (1951) referred to this type of change in myelosclerosis. It is, however, a more marked feature of osteopetrosis and I have seen it in a case of healing osteomalacia, but in these diseases other distinguishing features are present.

A woman was admitted for treatment of pyelitis. An enlarged spleen was noted and blood examination suggested the possibility of myeloid leukæmia. The sternum was so sclerosed that marrow could not be aspirated, so myelosclerosis was considered probable. A bone biopsy confirmed this diagnosis and the specimen showed marked increase in the size and irregularity of trabeculation. Skeletal survey films show generalized increased density of the pelvic bones and there are ill-defined sclerotic areas present in the right upper femur. The granularity and loss of trabecular pattern is noted in the ischium and pubis (Fig. 2A) when compared with a normal control of the same region (Fig. 2B). In the femoral neck (Fig.)

there is increased prominence of the weight-bearing trabeculæ. The upper humerus (Fig. 4), also shows hazy sclerosis with disordered trabeculation and ill-defined areas of porosis are also present. The appearance here could possibly be confused with metastatic deposits if complete skeletal films were not examined.

The next case also shows changes mimicking secondary deposits. Small dense areas are present in the centres of the vertebral bodies (Fig. 5). Similar areas of increased density are also present in the lower humerus (Fig. 6). The remaining skeletal films of this case show changes more indicative of myelosclerosis than metastases.

Splenomegaly is found in all cases, but in considering the differential diagnosis we must remember that splenic enlargement is also associated with bone changes in many other conditions.

In myelosclerosis the internal architecture of the bones may be altered in varying degrees so that radiological changes may be absent, slight or marked depending on the amount of new bone deposition upon the trabeculæ. The symptoms of the disease appear to depend on the extent of marrow fibrosis and the effectiveness of extra-medullary hæmatopoietic activity. Full skeletal survey films to include the skull should be done in all cases where sternal marrow aspiration proves impossible and whenever an enlarged spleen, together with

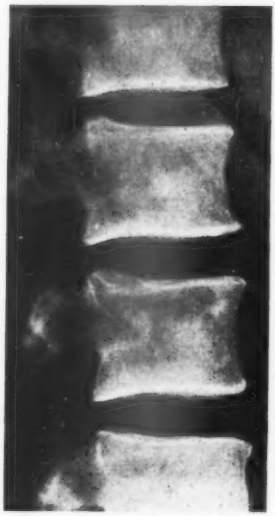


FIG. 5.—Lumbar vertebræ showing rounded dense areas in the centres of the vertebral bodies.



FIG. 6.—Lower humerus containing ill-defined areas of sclerosis.

any alteration in the bone texture, is noted in a patient past middle age. Control films should be used if necessary. When changes such as I have described are found, the case is probably one of myelosclerosis.

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I wish to thank Dr. E. Duff Gray, Director of Diagnostic Radiology, Manchester Royal Infirmary, for his help and encouragement, also Dr. B. J. Leonard, Dr. M. C. G. Israëls and Dr. J. F. Wilkinson of the Department of Hæmatology, for their valuable assistance and for allowing me to study their cases. I am grateful to Dr. R. G. W. Ollerenshaw and The Department of Medical Illustration for the reproduction of the radiographs, and to the staff of the Department of Pathology for the photomicrographs.

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Section of Anæsthetics

President—KATHARINE G. LLOYD-WILLIAMS, C.B.E., M.D., F.F.A.R.C.S.

[*October* 5, 1956]

Electroencephalography in Relation to Anæsthesia [*Abridged*]

REGISTRARS' PRIZE ESSAY

By SHEILA M. WILSON, M.B., F.F.A.R.C.S., D.A.

THE electroencephalogram is the record obtained using indirect leads of the changes in electrical potential taking place in the grey matter of the cerebral cortex, the electrodes being placed at two points on the scalp.

PHYSIOLOGICAL BASIS OF THE ELECTROENCEPHALOGRAM

At rest the electrical discharge from the cortical cells results in a wave pattern with a frequency of 9–10 cycles/second and amplitude of 50 microvolts (Fig. 1A). This type of record is produced by a whole mass of cells discharging synchronously at approximately the same rate. If the electrical activity were produced by smaller groups of cells discharging asynchronously and at different rates, the resulting record would consist of innumerable irregular excursions rather than a recurring pattern. This, in fact, occurs in the recordings made during mental activity, especially visual activity where the large regular alpha waves are replaced by small irregular oscillations (Fig. 1B).

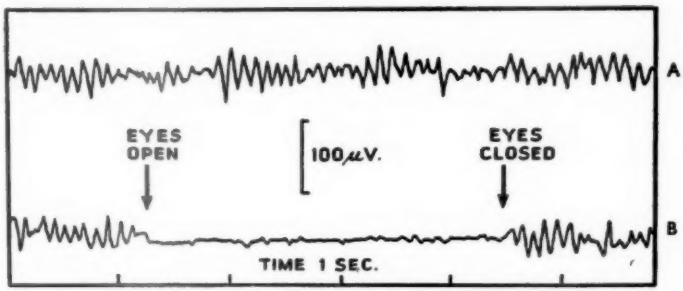


FIG. 1.—(Reproduced from Wright, S. (1952) by kind permission.)

Experimentally it has been shown that the resting discharge is due to the existence of a closed circuit between cortex and thalamus—impulses from the cortical cells reach the thalamus, cause an electrical discharge from the thalamus, which in turn stimulates the cortex again. Each time the circuit is traversed the cortical discharge produces the wave form recorded in the electroencephalogram.

In certain states of anæsthesia the cortical potential waves occur in groups separated by intervals of inactivity. Appropriate stimulation of the medial thalamus during a silent interval can set up typical runs of alpha waves in the cortex. This response occurs in areas of cortex which are connected only by thalamo-cortical fibres, so that the pathway between thalamus or cortex is a direct one.

These findings suggest that at the level of anæsthesia associated with periods of suppression of cortical activity there must be a depression at some point in the cortico-thalamic circuit. As the cortex remains capable of responding to stimuli, this depression must occur at thalamic level or below; that is, either the thalamus is not capable of responding to its normal stimulus or that thalamic activity is normal but the stimulus is depressed.

CLINICAL ELECTROENCEPHALOGRAPHY

In neurological investigations it is necessary to take simultaneous recordings from several leads to cover cortical activity over as wide an area as possible. This requires the use of multi-channel amplifiers with the electrodes placed on the scalp and connected in pairs to give antero-posterior and transverse cross-sections of activity in all areas.

For descriptive purposes the frequency spectrum from 1–30 cycles/second is as follows:

1–3·5	cycles/second	—delta	waves
4–7	,,	—theta	,,
8–13	,,	—alpha	,,
14–18	,,	—beta	,,
20–30	,,	—gamma	,,

It is the alpha rhythm of 8–13 cycles per second which predominates in the normal adult at rest, but there is a wide variation in the normal pattern between different individuals.

Under anæsthesia the individual variation disappears even in those patients who show abnormal records. This simplifies the study of the electroencephalogram during anæsthesia, as a single-channel machine with unilateral fronto-occipital leads can be used.

The Electroencephalogram under Anæsthesia

An early investigation of electroencephalographic activity during anæsthesia was carried out by Faulconer and his associates (Faulconer *et al.*, 1949) who demonstrated a correlation between depth of anæsthesia with nitrous oxide and changes in EEG activity.

Using ether, Courtin *et al.* (1950), showed that the electroencephalographic pattern varied with different levels of anæsthesia in a well-defined manner, and that it was possible to describe seven levels of anæsthesia on this basis (Fig. 2). The pattern present at any particular

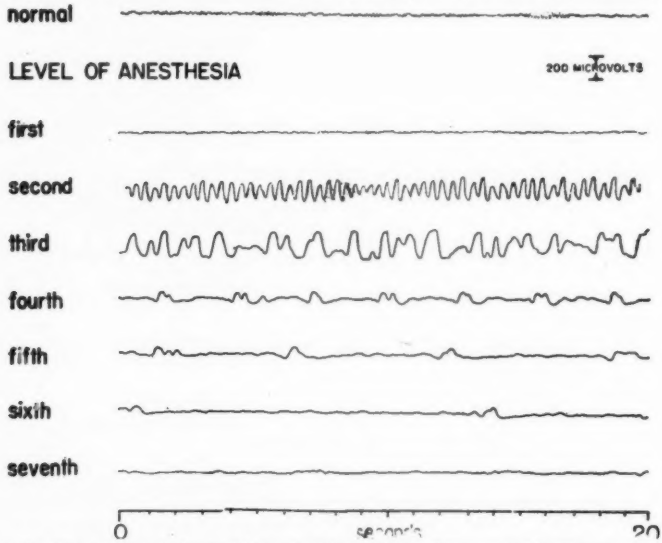


Fig. 2.—Electroencephalographic levels of anæsthesia (Nitrous oxide–Oxygen–Ether). (Reproduced from Courtin *et al.* (1950), by kind permission.)

time could be recognized as representative of one of these levels. As a measure of the depth of anæsthesia the electroencephalogram shows the direct effect of the drug in contrast to the accepted clinical signs of anæsthesia which are the peripheral effects of central depression.

An almost linear correlation between electroencephalographic level and arterial ether concentration was found from eighty-four observations (Faulconer, 1952; Bellville and Artusio, 1955). Ether in the presence of a nitrous oxide concentration exceeding 10 mg.% produced a deeper electroencephalographic level of anæsthesia than was obtained with the same concentration of ether alone.

Electroencephalographic activity under cyclopropane (Possati *et al.*, 1953) and sodium thiopentone (Kiersey *et al.*, 1951) has been studied, and well-defined electroencephalographic levels are demonstrated. The author has compared the steroid anæsthetic agent Viadril with sodium thiopentone, and the pattern sequence was found to be similar. Of other commonly used drugs, morphine, pethidine and muscle relaxants produce no effects on the electroencephalogram, when used in normal doses.

Effect of Anoxia on Electroencephalographic Activity

Many workers have shown, both in man and animals, that anoxia in the absence of anæsthesia produces marked alteration in the encephalogram (Sugar and Gerard, 1938; Gibbs *et al.*, 1940; Amyers *et al.*, 1953).

Under anæsthesia it can be shown experimentally (Beecher *et al.*, 1938) that there is little effect on cerebral activity until a level of 40% oxygen saturation in arterial blood is reached (in the presence of a normal carbon dioxide tension); below this level cortical depression rapidly supervenes. This is a marked fall of oxygen saturation; as it has long been accepted that cerebral cells are extremely sensitive to oxygen lack, the explanation may lie in a compensatory mechanism controlling the cerebral circulation. It can be shown that there is a reduced cerebral arteriovenous difference in states of anoxia. Assuming that oxygen requirements remain the same, this indicates an increase in total cerebral blood flow.

Carbon Dioxide Tension and Cerebral Activity

It is accepted that a high arterial carbon dioxide tension becomes a narcotizing agent and that this effect is potentiated by the presence of barbiturates and other anæsthetic agents. It has been shown, both in man and animals (Clowes *et al.*, 1953), that this depressant effect is reflected by alteration in electrical activity of the brain.

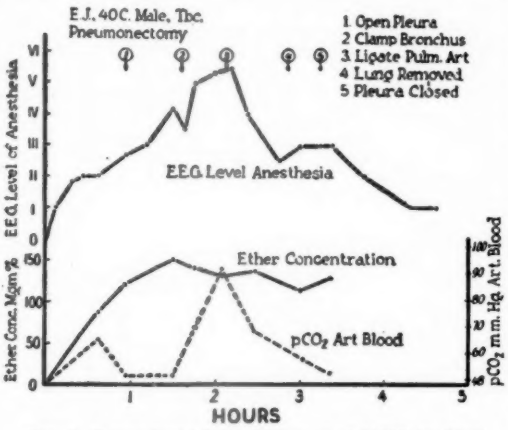


FIG. 3. (Reproduced from Clowes *et al.* (1953) by kind permission.)

The value of the electroencephalogram in demonstrating the depressant effect of carbon dioxide has been shown clinically in a patient undergoing pneumonectomy under ether anæsthesia (Fig. 3). The EEG showed the pattern of anæsthetic level IV, with a normal carbon dioxide tension. When the bronchus was clamped, leaving the vessels intact, the blood carbon dioxide tension rose rapidly to 94 mm.Hg and, in spite of a slight fall in blood ether concentration, the EEG pattern altered to level V and practically to level VI. Shortly after ligation of the pulmonary artery the tension of carbon dioxide fell from 94–68 mm.Hg and the EEG pattern returned to level III.

Effect of Hypotension

The EEG pattern under hypotensive conditions depends on the actual blood pressure and the rate of fall. At a rate of under 10 mm.Hg/min. a fall of 100 mm.Hg may produce no electroencephalographic change. Rapid, although smaller, decreases in blood pressure can produce slow, high amplitude waves or even temporary cessation of activity. These findings may be explained by assuming that cerebrovascular resistance is unable to accommodate to very rapid falls in blood pressure, and a fall in cerebral blood flow occurs. The resulting anoxæmia produces depression of the EEG; recovery occurs as the cerebrovascular resistance decreases, causing increased blood flow, even though blood pressure remains low. When the blood pressure is reduced slowly the cerebrovascular resistance may decrease as the blood pressure falls, so that cerebral blood flow remains constant and the EEG is not altered.

We have shown, using the EEG, that sodium thiopentone acts for a much more prolonged period under induced hypotension than in the normotensive state; in one patient where the systolic pressure had been reduced from 110–55 mm.Hg, 125 mg. of sodium thiopentone caused a depression from level I to level II which did not return to level I for thirty minutes.

Effect of Hypothermia

Reduction of body temperature to reduce oxygen requirements has become an accepted technique of anæsthesia. Little change occurs in cerebral activity until the temperature reaches 31°–35° C., when some decrease in amplitude and frequency occurs.

At 25° C. the voltage is further decreased. At 20° C. there is no appreciable activity in either parietal or occipital regions and only a slight wavering of the base line at 2 cycles/second in the frontal region.

Repeated cooling or prolonged maintenance at low temperatures does not alter the pattern. During rewarming no new rhythm appears and the changes of cooling appear in the reverse order but with a lag of 1° to 2° C. The return to normal EEG pattern confirms the clinical findings that no permanent brain damage is sustained at these low temperatures.

THE VALUE OF THE EEG IN CIRCULATORY ARREST (Bellville *et al.*, 1955*a*, *b*)

Following arrest of the circulation the first cells to suffer permanent damage are those of the cerebral cortex. It is recognized that if cardiac massage is to lead to a successful outcome an adequate circulation must be instituted within three minutes.

We have confirmed the value of the electroencephalogram in a case of cardiac arrest in an infant during thoracotomy under hypothermia. Fig. 4A shows the EEG pattern prior to circulatory arrest when the body temperature was 29° C. Within a period of 12 seconds following arrest virtually all electrical activity ceased (Fig. 4B) but activity could be restored to the pre-circulatory arrest pattern by cardiac massage (Fig. 4C). The interval between cessation of the circulation and alteration in pattern is rather longer than in other cases reported (Bellville *et al.*, 1955*a* and *b*), probably due to the reduction in oxygen requirement by the cortex at low body temperature. While it is possible to cut off the circulation in a patient at this body temperature for a period of 8 minutes without causing any permanent cerebral damage, it is interesting to note that cerebral electrical activity becomes negligible immediately the circulation ceases. Circulatory occlusion, in a patient at normal temperature,

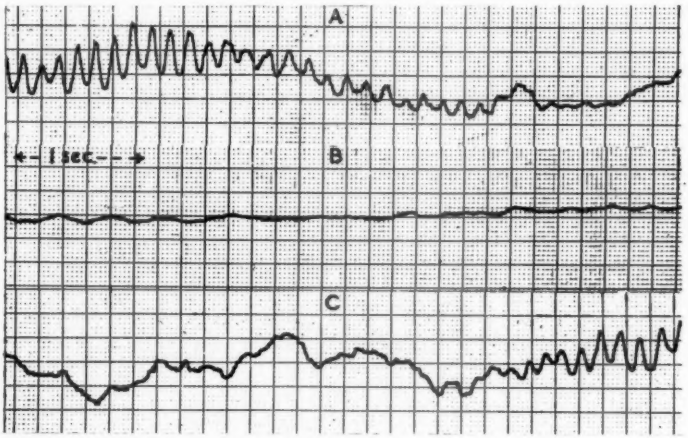


FIG. 4.

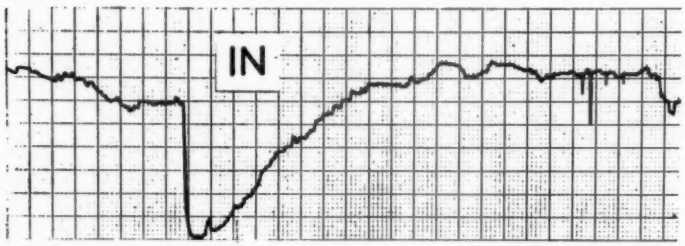


FIG. 5.

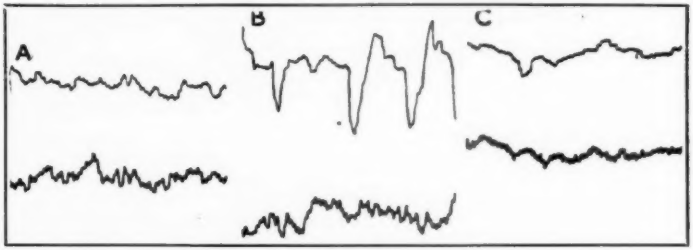


FIG. 6.

produces the same effect on the encephalogram, but in this case the changes are irreversible if present for more than a brief period. In the case reported the longest period of complete inactivity in the electroencephalogram was 1 minute 45 seconds.

The electroencephalographic changes in circulatory arrest are sufficiently rapid to allow the surgeon immediately to assess the efficiency of cardiac massage.

The sensitivity of the electroencephalogram during the cessation of the circulation has been demonstrated during the course of mitral valvotomy. During the brief period of occlusion of the orifice of the mitral valve the record becomes momentarily abnormal, but returns to the normal picture immediately the circulation is restored (Fig. 5). The reason for the alteration in EEG recording being even more rapid than in cases of cardiac arrest is not known.

We have also made use of the electroencephalogram to determine the adequacy of the circulation during operation on a carotid body tumour. Here we used a twin-channel machine, using fronto-occipital leads on each side. During the initial part of the operation the records were similar, as would be expected (Fig. 6A). A fall of blood pressure from 110–55 mm. Hg systolic, produced by Arfonad and posturing, in twelve minutes did not alter the pattern. During dissection of the tumour, with partial occlusion of the common carotid artery, the corresponding record became dominated by slow waves up to an amplitude of 50 microvolts (Fig. 6B). These resulted from anoxæmia. No additional anæsthetic drug had been administered nor was there any alteration in blood pressure, the record on the normal side remaining the same as at 6A. Application of the clamp to the common carotid for one minute produced increased cortical suppression in the affected hemisphere (Fig. 6c). Recovery did not occur during one minute following its removal. During the ten-minute period following ligation of the vessel an increase in cortical activity on the affected side occurred with loss of the periods of suppression, decrease of the high voltage low frequency waves and reappearance of fast activity.

Following operation this patient remained drowsy for a period much greater than would be expected from the total dosage of depressant drugs. The following day he complained of severe headache, confined to the affected side. Both these effects were probably the clinical manifestation of the period of cerebral anoxia. No permanent brain damage ensued, nor had this been expected from the brief duration electroencephalographic findings.

SUMMARY.—(1) The physiological basis for the electroencephalogram is described. (2) The value of encephalography in anæsthesia is described in relation to the usual anæsthetic agents. (3) The effects produced by anoxia, carbon dioxide, hypotension and hypothermia are discussed. (4) Cases are reported of the use of the electroencephalogram in various forms of circulatory disturbance.

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The Role of Posture in Laminectomy [*Abridged*]

REGISTRARS' PRIZE ESSAY

By D. J. PEARCE, M.B., F.F.A.R.C.S., D.A.

TROUBLESOME hæmorrhage has always been a consistent feature during laminectomy, often making adequate exploration of the vertebral canal and nerve roots impossible. Hæmorrhage can occur at all stages of the operation: initially, from the superficial tissues and muscles and, later, from the cut spinous processes and laminæ and the epidural veins. The blood loss during operations on the spinal column and cord varies from 658 ml. to 992 ml. (Bonica and Lyter, 1951).

In the efforts to combat this problem many techniques have been used; originally local infiltration (Freiberg and Perlman, 1943) was carried out, but more often to obviate the deleterious effects of ether anæsthesia rather than to reduce blood loss. Other workers used spinal anæsthesia (Nitikman, 1945; Hunter, 1950), pointing out that the blood-pressure fall and degree of muscle relaxation provided ideal conditions. Similar arguments have been advanced in favour of epidural anæsthesia (Bromage, 1952). Further progress was made with the introduction of the hypotensive agents of the methonium series (Davison, 1950;

Enderby, 1950; Organe, 1950; Scurr, 1951) and Arfonad (Magill, Scurr, and Wyman, 195), although Wyman has pointed out the inconsistency of results with these methods. Oth r workers have shown that, despite the attenuation of bleeding from the superficial tissues w h the use of these drugs, considerable hæmorrhage could still occur from the deeper structu s (Rollason, 1953).

Closely associated with this is the problem of posture; for bilateral explorations of t e vertebral canal the prone position has been advocated (Pennybacker, 1950), providing th t an efficient suction apparatus is available to keep the operative field clear of blood. Th s disadvantage has caused many workers to adopt the lateral posture, so that blood tends o run out of the wound rather than collect in the depths of a cavity.

From our study of 80 cases of lumbar laminectomy it was evident that the operative co - ditions were extremely variable. The anæsthetic methods included spinal, epidural—wit h and without the addition of adrenaline hydrochloride solution—and general anæsthesia, th e latter with and without the use of hypotensive drugs. Both prone and lateral positions wer e employed. Even with the use of pentamethonium iodide or Arfonad, which in most case s considerably reduced bleeding from the superficial tissues, it was apparent that difficulty ha d often been experienced in identifying the disc lesion owing to troublesome hæmorrhage fro m the deeper structures. Comments such as, "Persistent ooze from the raw, bony surfaces", or, "Troublesome bleeding from epidural veins", were only too common in the anæsthetic notes. It was also noted that post-operative oozing from the wounds and hæmatoma formation occurred frequently. That the latter is a well-recognized complication is a fact also borne out by other workers (O'Connell, 1951). In view of the disappointing discrepancy in these results it was felt that a further study should be carried out.

Methods of Study

Since it was realized that the chief difficulty was venous oozing, the studies were directed towards the elimination of inferior vena caval compression, the cause of the congestion.

(1) *Anatomy of the venous drainage of the lumbar vertebræ and vertebral canal.*—The vertebral bodies contain and are surrounded by an extensive network of veins, forming a vast potential venous reservoir. All of these vessels, together with venous channels from the vertebræ themselves, drain into segmental intervertebral veins which accompany the spinal nerves through each foramen and thence to the lumbar veins. The drainage of the lumbar veins, of which there are five pairs, is variable. The third and fourth pairs end in the inferior vena cava, while the first and second pairs either drain into the inferior vena cava or the ascending lumbar vein. The latter is a vessel which passes upwards on the roots of the transverse processes, anastomosing with the ilio-lumbar vein below and connecting together the other lumbar veins; it also receives tributaries from the anterior external vertebral plexus. The fifth pair of lumbar veins drain into the ilio-lumbar veins.

(2) *Venous pressure measurements.*—Venous pressure measurements were taken from the lower end of the inferior vena cava by means of a cardiac catheter connected to a simple water manometer. Six series of results were obtained (Table I). In each case it was clearly

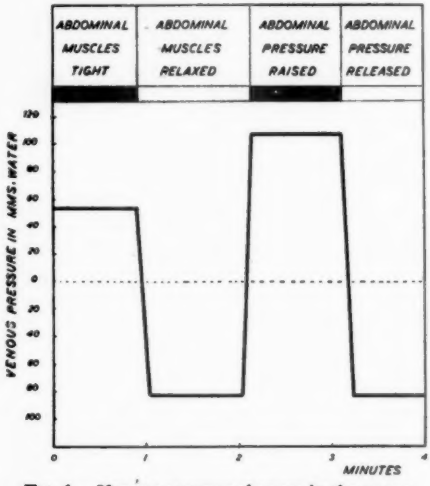


Fig. 1.—Venous pressure changes in the prone supported posture.

Table I.—Venous Pressure Changes in the Prone Supported Posture
(Maximum Readings in mm. H_2O)

Case No.	With abdomen hanging free	With abdomen compressed
1	10–25	170–200
2	45	180
3	0–15 0–10	300+
4	0–25	150
5	40	115
6	–80	110

demonstrated that pressure on the abdomen, sufficient to cause obstruction of the inferior vena cava, produced a remarkable rise of venous pressure, in some cases to more than 300 mm. H_2O. Even the slightest compression caused a rapid increase of 30–40 mm. H_2O, a rise of pressure probably large enough to distend the thin-walled epidural veins.

In comparing the different postures it was found that the lowest corrected venous pressure (−80 to +45 mm. H_2O) occurred in the prone position with a large bloc

under the chest and several small sandbags under each anterior superior iliac spine; by using muscle relaxants the abdominal wall was allowed to hang quite freely and clear of the table surface (Fig. 1). Using controlled respiration, however, it was essential that no build-up of carbon dioxide occurred nor increase of pressure during the expiratory phase, as this caused a rapid rise of venous pressure. With the return of spontaneous respiration and contraction of the abdominal muscles an average increase of pressure of approximately 100 mm. H_2O occurred and this rose even higher if the patient was allowed to strain.

(3) *Histology of the epidural veins.*—These veins are thin-walled (Franklin, 1937), contain little or no muscle tissue, and valves are present in only a few of the smaller channels, so that the slightest rise in venous pressure will cause distension.

(4) *Dye injection studies in the cadaver.*—Harris (1941) has drawn attention to the original papers describing the anatomy of the spinal and vertebral veins. The classical paper by Batson (1940) on the metastatic spread of prostatic carcinoma re-emphasized the rich anastomoses of the vertebral plexuses with the inferior vena cava. Furthermore, from his experiments on cadavers and live monkeys he was able to show that a rise of intra-abdominal pressure, sufficient to produce compression of the inferior vena cava, caused radio-opaque dyestuffs to pass into the vertebral system of veins.

This experiment was carried out in the human cadaver, colloidal barium sulphate solution being injected through a cannula in the deep dorsal vein of the penis and serial X-ray films taken. Without obstruction the dye flowed easily along the inferior vena cava (Fig. 2), but when this was ligated the barium was seen to pass into the anastomotic channels (Fig. 3).



FIG. 2.—Normal flow of radio-opaque dye along the i.v.c. Antero-posterior view.

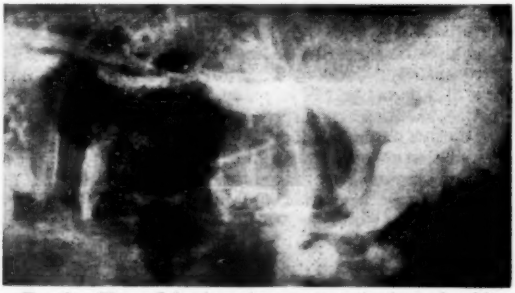


FIG. 3.—Flow of dye into the anastomotic channels with the i.v.c. ligated. Lateral view.

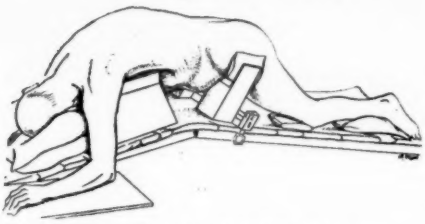


FIG. 4.—Position of patient for laminectomy.

From these results it became obvious that compression of the abdomen and inferior vena cava during laminectomy should be avoided at all costs, in order to eliminate completely the possibility of hæmorrhage from engorged epidural veins. It was also felt that reduction of hæmorrhage from the superficial tissues could best be achieved by infiltration with 1/250,000 adrenaline hydrochloride solution.

TECHNIQUE EMPLOYED

The standard principles of general anæsthesia are observed, using sodium thiopentone, nitrous oxide and oxygen, supplemented by pethidine and muscle relaxants as the anæsthetic agents. In these cases suxamethonium chloride, in drip form, has been used to provide muscle relaxation. Endotracheal intubation with a cuffed oral Magill tube is used in all cases to ensure complete control of the airway and to prevent aspiration of any regurgitated gastric fluids during positioning on the table.

The patient is placed in the prone posture with a large supporting block under the upper part of the chest and adjustable, well-padded supports under the anterior superior iliac spines (Fig. 4). In this way the abdomen is allowed to hang freely. The legs are lowered

slightly and the knees and ankles supported by soft pads. The hands are allowed to rest on stools, placed on each side of the operating table. A head-down posture is never allowed in patients who have recently had a myelogram.

To reduce bleeding from the superficial tissues a solution of 0·25% lignocaine hydrochloride with 1/250,000 adrenaline is used, according to the method described by the late Dr. Rait-Smith (1949) for chordotomy. Using a strictly aseptic technique, approximately 10 ml. of solution are injected down to the root of each lumbar transverse process in a fan-wise direction two fingerbreadths from the mid-line. In this way a barrier of solution is deposited in the muscles and in the angle formed between the transverse process and the lamina of the vertebra. Three spaces above and three spaces below the suspected site of the disc lesion are infiltrated on each side. Finally, a superficial mid-line skin wheal is raised at the site of the surgical incision. The total volume of solution used is 120–150 ml. The infiltration can be carried out either by the anæsthetist or the surgeon, as conditions permit. In case of superficial œdema caused by the infiltration, a scratch mark should be left at a predetermined site as a landmark for the benefit of the surgeon.

In some of the cases chlorpromazine hydrochloride was used in order to obtain the reversal of the adrenaline pressor reflex, but no real difference was noted in the results and it is not considered an essential part of the technique.

Results

A further 25 cases of laminectomy have been carried out using this technique. In all of them the operating conditions have been so outstanding that the use of Spencer-Wells forceps and diathermy has been entirely unnecessary and the suction apparatus rarely required. An extremely thorough exploration of the vertebral canal and nerve roots has been possible and yet, in many instances, the actual operating time has been reduced to thirty minutes. It was thought at first that the lack of flexion of the lumbar vertebræ would be a disadvantage, but in practice this is not so.

Also, the increase in the time allowed for the induction of anæsthesia, positioning and local infiltration has been more than offset by the reduction in the actual operating time.

Apart from one post-operative chest infection no complications have occurred. In each case the wound has healed by first intention and no hæmatomata or sero-sanguineous exudates have been encountered. The addition of 0·25% lignocaine hydrochloride to the solution used for infiltration appears to provide more immediate post-operative relief.

Although this series has been based on cases of prolapsed intervertebral disc, it follows, nevertheless, that this method can be employed in laminectomy for all other causes, except those in which sepsis is thought to be present.

Summary.—(1) The anæsthetic techniques employed in laminectomy in an attempt to provide a bloodless field for the surgeon are reviewed briefly and the discrepancy in operating conditions noted in a series of eighty cases. (2) The role of posture is studied by means of venous pressure measurements from the inferior vena cava, the histology of the epidural veins and dye-injection studies in the cadaver. (3) The method of anæsthesia used successfully in a further series of 25 cases of laminectomy is described.

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BOOK REVIEWS

Health in Industry: A Contribution to the Study of Sickness Absence: Experience in London Transport. (Pp. 177; illustrated. 35s.) London: Butterworth & Co. Publishers Ltd., on behalf of the London Transport Executive. 1956.

The late Lord Horder, in a foreword to this valuable study of sickness-absence statistics, gives a clear account of its origins. In the 1930's allegations had been made that the work of bus drivers and conductors was unduly exacting and injurious to their health. The matter was investigated by the Industrial Health Research Board of the Medical Research Council and Bradford Hill's report[1] was published in 1937. The statistical data available at the time were limited and incomplete, and the report was based on comparisons between illnesses of bus drivers and conductors lasting fifteen days or more in the years 1933–35, and those of tram drivers for the same period. As a result of conferences between representatives of the London Passenger Transport Board, the Transport and General Workers' Union and the Medical Research Council, the Board decided to strengthen its medical service and to make more satisfactory arrangements for recording particulars of sickness absence of members of its staff. It authorized the establishment of a Central Record of Staff Statistics, using punched cards, and records by this system have now been available since January 1948.

Dr. L. G. Norman, the Chief Medical Officer, and Mr. F. H. Spratling, Staff Administration Officer, describe how the records have been built up and how the data have been subdivided into broad diagnostic groups. It is encouraging to read that they are of the opinion that the diagnoses shown on medical certificates given by general practitioners are precise enough to justify their use as a basis for classification. A high degree of agreement has been found between the diagnoses by the London Transport doctors and those by the general practitioners.

Mr. F. H. Spratling contributes a closely reasoned account of the principles and methods followed in compilation of the statistics, together with explanations as to how they are to be used for comparison with other occupational groups. The major portion of the book (145 pages) is devoted to tables showing the actual and expected sickness-absence records in four main groups: (i) drivers and male conductors, central buses 1949–52; (ii) motormen and guards, London Transport railways 1950–52; (iii) male workshop staff, bus overhaul works 1949–52, and (iv) clerical and technical staff 1950–52.

It is not difficult to agree with the authors that the study of the incidence of sickness and disease, in all its forms, is of the highest importance; and with their hope that the London Transport statistics will be used by others who work in this field in order to make purposeful studies of the incidence of sickness absence in different occupations and employments. It is rather a pity that the reader is left to make his or her own conclusions as to whether this first batch of figures shows significant differences between groups or suggests the presence of occupational factors. The effect of age on sickness, however, is clearly shown.

The London Transport Executive and its staff are to be congratulated on their determined effort to put sickness-absence recording on a sound basis.

[1]Report No. 79 of the Industrial Research Board: An Investigation into the Sickness Experience of London Transport Workers, with Special Reference to Digestive Disturbances. London, 1937: H.M. Stationery Office.

Anæsthetic Accidents: The Complications of General and Regional Anæsthesia. By V. Keating, M.B., B.Ch., D.A., F.F.A. R.C.S. (Pp. vi + 261; illustrated. 25s.) London: Lloyd-Luke (Medical Books) Ltd. 1956.

Much of every anæsthetist's training and practice is devoted to the prevention of the accidents and complications which may so easily occur as the result of his administrations.

Any worth-while treatise on this subject must therefore embrace practically the whole range of the specialty. It must also consider at length the fundamental physiological processes of the body and how they may be disturbed by anæsthetic drugs and procedures, for only by a full understanding of these mechanisms may further disasters be avoided.

These criteria are fulfilled in this excellent treatise, which is far more than a mere chronicle of mishaps culled from the scattered literature. These many collected reports on the untoward sequelæ of every type of anæsthetic would in themselves make instructive reading, but their value is greatly enhanced by the author's wise comments on them. Much of our knowledge of physiology and pharmacology is derived from animal experimentation, but Dr. Keating is well aware that the conclusions drawn from such experiments are not always applicable to man in their entirety. He is careful to point out where our knowledge is incomplete, and here he is not afraid to make constructive suggestions based on his clinical experience. In the Preface this book is described as "an attempt to review the causes and to

indicate the possible prevention of . . . anæsthetic accidents". In this purpose the author has succeeded admirably and this well-produced little book deserves to be widely read.

The Care of the Expectant Mother. By Josephine Barnes, M.A., D.M.Oxon., M.R.C.P. London, F.R.C.S.Eng., F.R.C.O.G. (Pp. x + 270; illustrated. 30s.) London: Pitman Medical Publishing Co. Ltd. 1956.

The title of this excellent book is somewhat of a misnomer, for it gives the impression that here is merely yet another advisory handbook for the woman expecting her first baby. In fact it is a scientific textbook designed specifically for "all who undertake the management of pregnancy", and being written from a very practical angle throughout, it forms an excellent general guide to this subject.

The most revolutionary change in obstetric practice in the past thirty years has been in antenatal care, and there is little doubt that the dramatic improvement during that period in maternal and fœtal mortality is due mainly to careful medical supervision during pregnancy. Miss Barnes' book, based largely on clinical lectures to students and pupil midwives, gives the most complete account to date of how a pregnant woman should be cared for from conception to delivery. Almost every conceivable aspect of the subject is covered, from prenatal advice to radiological pelvimetry, and all are described successively and in a practical common-sense manner.

In handbooks of this nature, a certain amount of dogmatism is inevitable, but some of the author's statements are possibly too emphatic. Few obstetricians, for example, will agree that "abdominal examination is not strictly necessary before the 32nd week," or that it is a good thing to use Hegar's sign as a test for pregnancy. It is also doubtful whether massaging the breasts for two months to express colostrum before delivery may not do more harm than good, and the dangers of radiography to the fœtal gonads require constant emphasis to avoid unnecessary exposure. The book deserves general praise for its practical attention to the details of normal and abnormal pregnancy, and as such it will be invaluable not only to senior students and midwife teachers, but more particularly to general practitioner obstetricians, who will find here their complete vade-mecum.

Operative Surgery. Editors: Charles Rob, M.C., M.Chir., F.R.C.S., and Rodney Smith, M.S., F.R.C.S. In 8 volumes and index. (Volumes 1 and 2. Volume 1 Introductory, Surgery of Trauma, Abdomen (part); Volume 2 Abdomen (completion); illustrated. £5 10s. per volume.) London: Butterworth & Co. Publishers Ltd. 1956.

One has merely to glance at and handle these first two volumes of this projected 8-volume work to recognize that it has been conceived and produced on a noble scale. And the first task of any reviewer must be to congratulate both the editors and the publishers on this. In their introduction, the editors explain the principles they have followed. Operations are best learnt by watching, and therefore the principal emphasis of any operative surgery textbook should be visual. The text should be minimal, and largely explanatory of special points and difficulties. The work is chiefly intended for surgeons in training, surgeons working in an isolated community, and experienced surgeons called on to operate in an unfamiliar field. The potential surgical public is, therefore, a large one. The editors have chosen with care their contributors (judging by the contributors to these two volumes their choice will command general respect), and having done so they have largely relied on their judgment.

Three subjects are dealt with in the two volumes now under review—Part I General Technique, Part II the Surgery of Trauma and Part III the Abdomen. Part I contains much that might be compulsory reading for house surgeons, e.g. the choice of ligature material, the technique of intravenous infusions, and the tying of knots; the author of the latter is surely a fisherman. The chapters on the Burst Abdomen and Radium Needle Insertion seem, however, rather out of place. Part II consists of an excellent series of articles on the treatment of trauma. Relatively small points of criticism are that only surgery is considered in the treatment of heart tamponade and no mention is made of aspiration; and that the débridement of wounds is stated to be contra-indicated if more than eight hours have elapsed since the wound was inflicted. In Part III on the abdomen, one notes the article by Tanner on Gastrectomy with all his numerous tips for dealing with difficult ulcers. And your reviewer found the article by Milnes Walker on porta-caval anastomosis a useful test, since it is not an operation he has performed or seen performed, and he would be much more confident in performing it now. In the chapter on partial hepatectomy, however, one is a little surprised not to see right lobe hepatectomy described as well as left lobe hepatectomy.

Full judgment on the work must obviously await the appearance of the further six volumes. But first reactions are that the editors and publishers are establishing their case, and one ventures the prophecy that the work will have a big sale throughout the world and in so doing will advance still further the prestige of Great Britain and of European culture in general.

Clinical Section

President—Sir HENEAGE OGILVIE, K.B.E., D.M., M.Ch., F.R.C.S.

[*November* 9, 1956]

The Solution of a Surgical Dilemma.—GEOFFREY FLAVELL, F.R.C.S., M.R.C.P.

The patient is a police inspector aged 43. In 1933 he had a left spontaneous pneumothorax, which recurred in 1937. Mass miniature radiography in 1953 revealed a very large emphysematous bulla at the apex of his right lung occupying much of the pleural space. The left apex was hypertranslucent (Fig. 1). I advised excision of the air cyst but as he was symptom-

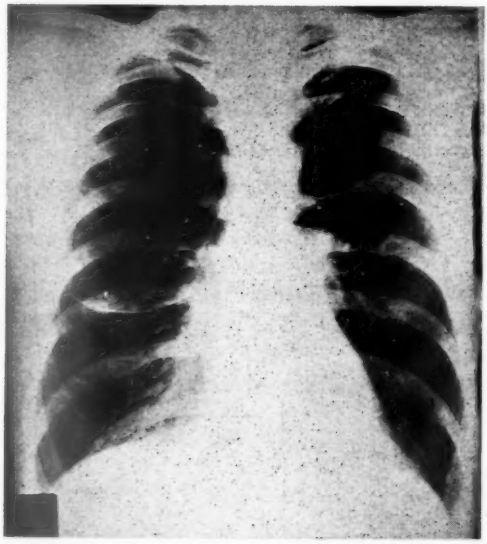


FIG. 1 (January 1955).—The initial state of the patient's chest with the whole of the upper part of the right lung displaced by two enormous bullæ. Note the hypertranslucency also present at the left apex.

less he refused, but he continued to attend the follow-up clinic at six-monthly intervals. The bulla did not increase in size. He remained well until August 1955 when for the first time he noticed breathlessness, and a little later developed a cough productive of purulent sputum. This was followed by fever and hæmoptysis. X-rays of his chest revealed a patchy opacity spreading over most of the upper lobe of the left lung (Fig. 2). At first this was thought likely to be inflammatory, and following antibiotic therapy it resolved largely—*but not wholly*. As a diagnosis of "unresolved pneumonia" is unacceptable the patient was bronchoscoped, and a bronchial carcinoma was found growing from the left upper lobe orifice.

Left pneumonectomy was out of the question; and even if upper lobectomy had been technically possible it could not have been undertaken with so much of the opposite lung compressed by an enormous alveolar cyst. It was therefore decided:

(1) to treat the growth with deep X-rays in order to render lobectomy feasible, and

(2) to operate first upon the right lung to remove the bulla and so to secure maximum efficiency;

(3) then to operate on the left lung and remove the growth.

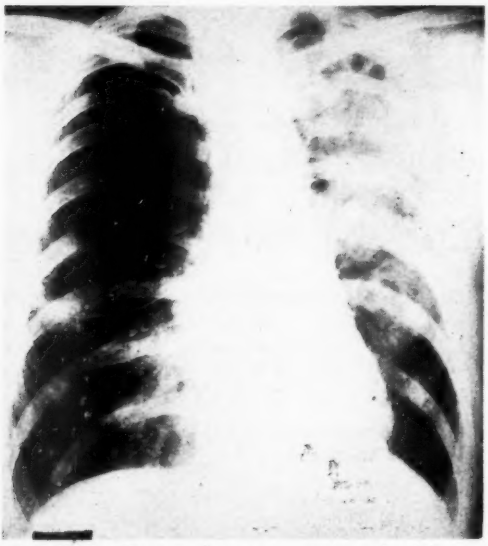


FIG. 2 (October 1955).—The opacity now present at the left apex is due to infection occurring distal to bronchial obstruction caused by a neoplasm.

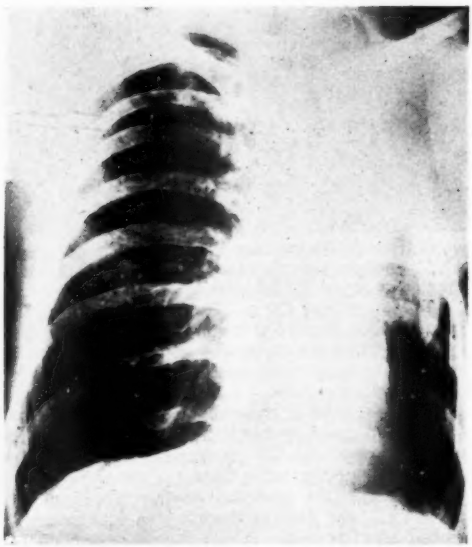


FIG. 3 (June 1956).—The bullæ have been removed from the right lung which is now totally re-expanded. The left upper lobe containing the neoplasm has been removed and an apical thoracoplasty performed to preserve the left lower lobe from increasing emphysema.

By the beginning of February 1956 bronchoscopy showed the growth to have regressed and to be now operable by lobectomy. On 6.2.56 two very large bullæ with a volume of about 1 litre were excised from the upper lobe of the right lung, the anterior segment of which was spared. Post-operatively so much air leakage occurred from the raw area of emphysematous lung left behind that the patient developed a *tension pneumothorax* in spite of two drainage tubes attached to continuous suction pumps; and it was not until four pumps were put in line that the right lung completely re-expanded to fill the pleural cavity. Following this operation dyspnœa was wholly relieved—in fact the patient has never been breathless since—and bronchospirometric studies showed his respiratory efficiency to have improved by 50%.

On 20.2.56 the left chest was opened, and the upper lobe of the lung removed without difficulty. On section, residual strands of polygonal cell carcinoma were found beneath the bronchial mucosa, but no growth reached to the cut end of the bronchus or was found in the regional glands. During the next few weeks the left lower lobe showed signs of increasing emphysema, so on 19.3.56 a left apical thoracoplasty was performed (with removal of the 2nd, 3rd and 4th ribs) to obliterate dead space and prevent over-expansion of the lower lobe (Fig. 3).

By June the patient was completely well, working, and suffering not at all from breathlessness. Bronchoscopy showed the site of amputation healthy with no evidence of recurrence.

In September he complained of a persistent occipital headache and, suspecting a metastasis, I referred him to my neurosurgical colleague Mr. J. Crawford. On 12.9.56 ventriculography confirmed this diagnosis and on the same day Mr. Crawford performed a posterior fossa craniotomy and removed a well-defined secondary deposit of bronchial carcinoma 3×3×2 cm. from the right lobe of the cerebellum. There was no evidence of any other deposits.

The patient was ambulant two weeks after operation and has made an uninterrupted recovery.

The following cases were also shown:

Chronic Lymphatic Leukæmia Treated with C.B. 1348.—Dr. R. J. HARRISON and Dr. D. A. G. DALTON.

Coronary Insufficiency: Implantation of Internal Mammary Artery.—Dr. J. C. FIRTH (for Mr. C. E. DREW and Dr. R. J. HARRISON).

Mitral Stenosis—Hæmosiderosis, Ossified Pulmonary Nodules—Valvotomy.—Dr. R. J. HARRISON and Mr. C. E. DREW.

Sarcoma of Leg.—Mr. L. DE JODE (for Mr. HERMON TAYLOR).

Spontaneous Hæmopneumothorax.—Dr. B. B. REISS (for Dr. R. J. HARRISON).

Two Cases of Spontaneous Rupture of the Spleen.—Dr. G. H. LUCAS (for Mr. W. D. PARK).

[*December* 14, 1956]

The following cases were shown:

Subdural Hæmatoma Referred as a Mental Case.—Dr. RICHARD ASHER.

Allergic Rheumatism, with Pulmonary Infiltration.—Dr. K. P. BALL.

? Collagen Disease. ? Atypical Virus Meningitis.—Dr. IAN FERGUSSON (for Dr. GERALD SLOT).

Long-standing Vascular Renal Tumour associated with Malignant Hypertension.—Dr. D. N. PHEAR (for Dr. K. P. BALL).

Solitary Actinomycosis of the Ulna.—Mr. G. S. PLAUT (for Mr. W. H. GERVIS).

Carcinoma of Stomach and Chronic Pancreatitis treated by Partial Gastrectomy and Pancreatico-Duodenectomy.—Mr. J. O. ROBINSON (for Mr. B. H. PAGE).

Scleroderma.—Dr. S. SEN (for Dr. GERALD SLOT).

Cushing's Syndrome—Surgical Aspects.—Mr. NORMAN C. TANNER and Dr. R. J. HARRISON.

Achalasia with a large Œsophageal Diverticulum.—Miss M. C. WATERFALL.

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(*Continued from p. 104*)

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United Services Section

President—Sir CECIL WAKELEY, Bt., K.B.E., C.B., F.R.C.S.

[*October* 11, 1956]

DISCUSSION: LEPTOSPIROSIS IN MALAYA

Lt.-Col. D. G. Levis:

Leptospirosis among Troops Operating in Malaya during 1954 *and* 1955

Introduction.—Leptospirosis is of widespread occurrence throughout the world [1]. This has perhaps not always been as well appreciated as it might have been. The variability of the clinical picture and the large number of distinct antigenic strains of leptospiræ responsible may perhaps have come as a surprise to those of us whose concept of the disease had hitherto been that of the severe illness originally described by Weil in 1886. Table I gives some idea of the variability of the disease and its nomenclature and, suggesting as it does a varied occupational ætiology and distribution, should remind us to suspect leptospirosis as being a cause of febrile disorders in many parts of the world.

TABLE I.—NOMENCLATURE: LEPTOSPIROSIS

Name	Infecting Leptospira
Weil's disease	*L. icterohæmorrhagiæ*
Canicola fever	*L. canicola*
Swineherds' disease	*L. pomona*
Mud/slime/water fever	*L. grippotyphosa*
Indonesian Weil's disease	*L. bataviæ*
Sejroe fever	*L. sejroe*
Seven-day fever	*L. hebdomadis*
Spirochætosis febrilis	*L. pyrogenes*
Cane fever	*L. australis A*

All these illnesses are generally characterized by fever, headache, myalgia and conjunctival injection but the hæmorrhagic, icteric and other prominent features of the classical disease may be lacking and there are often real difficulties in making a confident clinical diagnosis. In 1945 Buckland and Stuart reported cases of suspected Weil's disease among troops operating in N.W. Europe whose blood serum agglutinated with *L. sejroe* or *L. grippotyphosa* whilst giving no reaction to *L. icterohæmorrhagiæ* [2]. In 1949 Mackay-Dick and Watts were calling for an increased awareness of the manifestations of canicola fever in Germany [3]. In 1951 it was coming to be appreciated in Malaya that leptospiral infections with types other than *L. icterohæmorrhagiæ* were probably occurring in increasing numbers among troops engaged in jungle operations. The existence of leptospirosis in Malaya was, of course, known as a result of work by Fletcher in 1928. He demonstrated infection in man, dogs and various species of rats. He also showed the presence in human cases of *L. icterohæmorrhagiæ*, of several strains of *L. autumnalis* and *L. pyrogenes*. There were also others whose identity was not established at the time [4].

Military experience in 1954 and 1955 in Malaya suggested that infection with *L. icterohæmorrhagiæ* was the exception rather than the rule; and that leptospirosis could and did present a varied clinical picture. Unless it was specifically investigated as a cause of febrile illness it was likely to be missed and confusion with conditions such as dengue and scrub typhus was likely to occur.

Malaya in the two years 1954 and 1955 produced a certain total of 333 cases of leptospirosis from a military population which, over the period, remained virtually constant in size, composition and distribution. Leptospirosis is not a new disease to military populations.

The War of 1914–18 produced cases in what was described as mildly epidemic form in France and Flanders amongst both British and German troops. The majority of these appeared to be due to *L. icterohæmorrhagiæ* [5]. Operations in Europe in 1944–45 produced small outbreaks but the occurrence of other strains was noted [6, 2]. From a study

of available statistics, however, at no time during the whole of the 1939–45 War was anything approaching the number of cases which occurred in Malaya in 1954 and 1955 reported in any theatre: or indeed from all the British and Dominion troops engaged during the whole period. It was felt therefore that the Malayan experience of 1954 and 1955 was worthy of a closer study.

The pattern of incidence.—During 1954, 198 cases of leptospirosis from troops of all nationalities were admitted to military hospitals in Malaya: in 1955 this figure declined slightly to 135. These figures constituted 2·1% and 1·6% respectively of all admissions.

The mortality from the disease was low. There were only two deaths in the two-year period that could be confidently ascribed to leptospirosis. Many patients were, however, gravely ill; the majority were of mild to moderate severity and were incapacitated for about three weeks.

During the two-year period there was only one instance of the same individual contracting the disease twice. In this case the first infection was in April 1954, the second infection occurring in July of the same year. Between infections the individual remained well and at duty.

The temporal distribution of the cases in Malaya is shown in Fig. 1. It will be noted that cases occurred throughout the year. The apparent peaks of incidence were due to small outbreaks occurring in units operating in areas where experience showed a high endemicity.

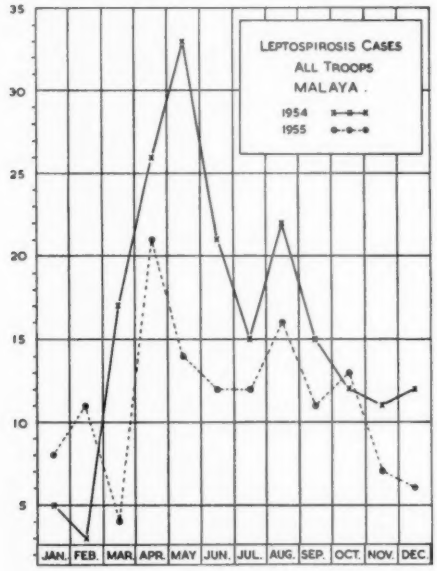


FIG. 1.

Although no convincing relationship to weather conditions was discoverable it was noted that the cases in Malaya were perhaps more obvious after a wet spell had occurred after a period of relative drought.

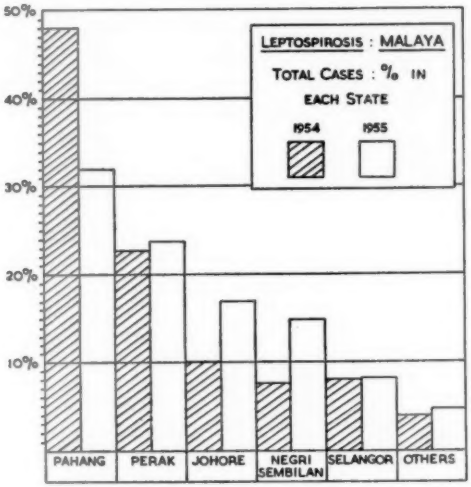
Australian workers have reported that in Queensland, which has an annual average rainfall of 60 in., cases of cane fever (*L. australis A*) generally showed an increase at the time of the peak rainfall (January, March) [7].

Geographical distribution.—When this was studied it was apparent that cases of leptospirosis could arise in nearly every State in Malaya. The number of the troops operating in each State varied with operational needs but when this number was studied against the number of cases of leptospirosis reported it became apparent that in at least two States there were areas where the endemicity of the disease was high, particularly the west central area of Pahang and the central area of Perak. There was a smaller and

rather subsidiary area about 10 miles out of Kuala Lumpur in Selangor, but it only attracted passing attention as operations therein were not continuous.

The existence of the disease in Perak was well known as a result of Fletcher's observations in 1928 but it was not until late 1953 that attention was focused on Pahang when a sharp outbreak occurred among British troops operating in the west central area of that State [12]. Fig. 2 shows the percentage distribution of cases of leptospirosis over the two-year period in each State.

In Trengganu and Malacca the number of troops in each State was almost negligible as they had been freed of trouble. The number operating in Kedah was small and in the main, Malay troops, while in Kelantan, apart from field engineer activities by a small unit, there was none. One feels fairly confident in saying, however, that, if larger numbers had been engaged in these States and operations had been extensive, cases of leptospirosis would have been noticeable.



OTHERS = KELANTAN, KEDAH, TRENGGANU, MALACCA, PROVINCE WELLESLEY.

FIG. 2.

It was the west central area of Pahang which had the evil reputation and no less than four British units at one time or other suffered in the same area. The high endemicity of this area was supported by the experience of two British units of equal size which performed almost identical operations in west central Pahang and Selangor having relieved each other. The attack rate for each was low while in Selangor, but increased sharply shortly after entry into Pahang. This observation can be underlined by the fact that the operations in Selangor entailed extensive patrolling of swamps which provided suitable opportunity for the contraction of infection. It occurred, but only sporadically.

Operational conditions and the distribution of cases amongst the troops at risk.—These two points may conveniently be discussed together. The following types of troops were engaged over the two-year period: British, Gurkhas and Malays who each formed a group of equivalent size; one battalion of Africans and one of Fijians, each of about the same size.

The administrative troops were based on the larger towns and worked from some permanent accommodation and never entered the jungle; the Armoured Corps had duties which, in the main, restricted them to road patrolling and convoy work with an occasional foray into the jungle. They were based on larger centres but had squadrons detached to the smaller country towns. The operational infantry operated as companies from semi-permanent camps in relation to the jungle fringe. From here they worked as small patrols returning to their company base after varying intervals to rest and refit before going out again. After a certain period each infantry unit would be withdrawn from jungle operations for a period of retraining in a major centre. The jungle work therefore fell on the infantry and the operations entailed prolonged and extensive patrolling, operations being

in primary or secondary jungle, scrub and swamp. While on patrol, troops lived on what they could carry or were maintained by a system of air supply. Water was found locally and instructions were that it should be boiled for tea or sterilized by individual outfits before drinking. In base camps and at unit H.Q.s fixed supplies were provided with filtration and chlorination under R.E. or unit arrangements. There is no doubt, however, that standards of water purification were uneven and patrols obtained water from indifferent sources. Washing facilities were primitive on patrol and it was not until return to base that individuals could achieve total skin cleanliness. The skin of the patrolling infantryman was rarely dry; sweat, rain, or both saw to that. Scratches and abrasions were inevitable in the thick secondary jungle where every kind of bush, creeper, thorn and bamboo abounded. Skin sepsis and fungus infections were encouraged by and flourished under such conditions. Strict insistence by regimental officers upon the prophylactic measures recommended could and did keep the skin troubles down, but they were there all the time.

The skin of the British soldier, particularly in the newly-arrived units, was liable to damage and infection; the Fijians generally had a high attendance on sick parades for minor skin troubles; the Gurkhas, Malays and Africans were affected but to a much lesser extent.

Such then were the general conditions under which troops of five nationalities operated in Malaya.

The leptospirosis experience of each group is given in Table II.

TABLE II.—DISTRIBUTION OF CASES BY RACE AND ROLE*

Role	British		Gurkhas		Malays		Fijians		Africans		Total
	1954–1955		1954–1955		1954–1955		1954–1955		1954–1955		1954–1955
Operational infantry ..	145	71	26	29	0	3	5	7	0	5	291
Others	14	14	2	5	4	1	—	—	—	—	40
Totals	159	85	28	34	4	4	5	7	0	5	331
Attack rate all troops per 1,000 per year ..	12·2		6·5	2·9	3·6	0·3	0·3	6·2	8·7	—	6·2	9·2

*This table does not include 1 Chinese liaison officer and 1 Dyak tracker who were attached to operational infantry.

Table II shows clearly that it was the operational infantry that sustained the majority of cases: the urban-based troops escaped lightly. When approximate attack rates per 1,000 men at risk were considered it was the British infantryman who suffered most, followed by the Gurkhas and the Fijians. Of all troops engaged, operational infantry or other, the soldier recruited in the country—the Malay—suffered relatively little.

It was first and foremost a disease of the jungle with the occurrence of sporadic cases in major urban centres or the more developed rural areas.

It is true that each of the areas noted as having a high endemicity contained a major British unit throughout the two-year period but, even after due allowance was made for this, the incidence among the British troops was still more noticeable. A Malay unit operated in west central Pahang simultaneously with a British unit over the period. They operated under identical conditions and in areas where leptospirosis was known to occur and yet the cases in this group were virtually nil. Taken overall, the number of cases of unexplained fever treated in the unit sick bays of Malay regiments was extremely small, as was the number admitted to hospitals for the same reason. Even if allowance is made that leptospirosis showed itself in its mildest form and passed unrecognized it is still considered that Malay soldiers were never seriously affected by leptospirosis. It is uncertain how far this reasoning can be applied to Fijians and Africans (both small groups) but it is possible that cases of fever with rapid recovery in both groups—which were retained in unit lines to a slightly larger extent than in the Malay group—may have included unrecognized cases of leptospirosis. The Africans operated in west central Pahang. The Fijians were in Johore.

The third big group, the Gurkhas, had a much lower incidence than the British. They may have been luckier in their operational areas. A group of cases (about six) did occur in a major infantry unit in an area of Selangor near Kuala Lumpur in 1955 and, for its size, the non-operational group of Gurkhas located mainly in well-developed camps and areas produced an attack rate nearly equivalent to the British non-operational group (approximately 2·3 per 1,000 per year Gurkha: 3 per 1,000 per year British). Gurkha susceptibility is hard to assess with any certainty.

Source of infection.—At various times animals such as rats, cattle, pigs and dogs have all been shown to harbour various strains of leptospiræ.

In Malaya there is a very large rodent population and at least three species of rat which

inhabit the primary jungle have been shown to be infected with leptospirosis [8]. In late 1955 two further species from camps in west central Pahang were also incriminated [9]. These last two were not primary forest rats by habit. They preferred secondary jungle, grassland or scrub, being abundant in the latter and in ladangs and areas of temporary cultivation. Rats therefore were in close relationship to the infantryman in his temporary jungle camps, his patrolling and ambush areas in the primary and secondary jungle and in his base camps.

Wild pigs in Malaya were also no strangers to the patrolling infantry, dogs were numerous in the ladangs and kampongs and certain of the British battalions employed tracker dogs with soldier handlers. Pig and buffalo wallows were far from rare. Possible additional sources of infection were not hard to find and mud, slime and water met in paddy-fields, swamps, rivers and streams were available to be contaminated.

Certain leptospiræ have recently been shown by Australian workers to remain viable for up to fifteen days in damp and acid soil [10]. Conditions in the Malayan jungles were probably equally suitable. A variety of leptospiræ were identified in Malaya from infections occurring among troops. There was no pattern to their distribution, west central Pahang provided a wide range and among the identifications carried out, icterohæmorrhagiæ ranked low in frequency. No cases were reported specifically among unit dog handlers, but that the dogs could at times be infected was appreciated. In only one patient was the infecting leptospira identified as *L. pomona* although wild pigs abounded in the scrub and swamp.

It is considered therefore that the main source of infection lay in the rodent population and that these were to be found in the temporary camps in the jungle, deeply buried ladangs, remote or deserted kampongs, deserted areas of cultivation or the swampy scrub encountered on patrol. Rats also infected the company base camps, but living conditions in the camps, although rough, offered less opportunity of contact with contaminated soil, and/or water. Secondary sources may have been wild pigs or numerous dogs.

Method of transmission.—It has long been accepted that contact with mud, slime, and water contaminated by the urine of the rodent or other animal harbouring the infection provides the opportunity for the leptospira to obtain access to the body. It may enter through damaged skin or through intact mucous membrane. Bathing in contaminated water provides other cases. In Malaya, in previous years, patients with leptospirosis have given histories of having bathed in local rivers or old mining pools [11].

Opportunity existed on patrols in jungle: skin abrasions were common: washing and bathing were done in rivers and streams while the standards of water purification were uneven. The importance of contaminated drinking water is stressed particularly when reliance had to be placed on individual methods of purification. The intermittent heavy rains could cause supplies available to patrolling infantry to be contaminated from surrounding areas and so reach individuals or groups. Contaminated drinking water could be the source of those infections which occurred among those whose duties kept them in the base camps with their more elaborate supply systems, the chlorination of which was apt to be irregular and to which rats had comparatively easy access. The origin of the cases in the administrative group is less easy to postulate. The few cases in the Malays could well have come as result of infection acquired during visits to their home kampongs where washing, bathing and drinking water supplies were less than ideal and the domestic economy productive of rats and stray dogs.

Prevention.—Under the conditions imposed by the operations in Malaya, it was impracticable to place a ban on certain areas or particular rivers and streams. The best that could be done was to try and reduce the risk of leptospiræ gaining access to the body. Skin hygiene therefore assumed an added importance while the safety of drinking and washing water supplies and the reduction or discouragement of the rats in company base camps were all stressed. Beyond that, one could do little.

Leptospirosis had become an occupational disease of the jungle patrol.

Discussion.—The occurrence of leptospirosis among the troops in Malaya showed that the disease was widespread in that country. Certain areas were revealed to be of higher endemicity than others. It can be said that the disease could probably be contracted in any State at any time of the year. It was a disease of the jungle patrolling infantryman rather than that of the supporting troops and it could be caused by any one of a large number of leptospiræ.

Mortality was low but it caused considerable incapacity among operational troops.

Series of cases occurred in units which gave the appearance of outbreaks but closer examination generally showed that the cases had occurred among several patrolling groups that had no common epidemiological factor except the general area of the country [12].

No cases could with certainty be ascribed to bathing in a particular river or pool or to using a particular water supply. The origin of the infection lay in the extensive rodent population of the jungle but secondary sources could possibly have been in the wild pig, dogs or buffaloes. The route of the infection was probably the consumption of contaminated water and the contact of abrased skin with contaminated mud, slime and water while on patrol. Of the three main groups the heaviest sufferer was the British soldier. The Malay, recruited in the country, suffered scarcely at all although oddly enough one of the two fatal cases was in a Malay. This suggests some degree of racial immunity. The Malays operated alongside British troops in areas of known high endemicity apparently with impunity. It must be appreciated that the system of National Service resulted in the constant dilution of the British units with "unseasoned" young men. The Malay Infantry on the other hand were a long-service group. Second infections in the same individual were rare so it is conceivable that some immunity can be acquired. The Gurkhas, the third of the large groups, were also long-service soldiers, with continuous service in Malaya for some years. They, although they suffered more than the Malays, did not approach the British in susceptibility.

Of the two small groups, the Fijians, who were diluted with drafts at intervals, seemed to suffer along with the British. The Africans, who were not diluted during their tour, were much less susceptible even though they operated continuously in an area of high endemicity. It seems possible therefore that the longer a unit stayed in Malaya, provided its composition remained stable, its chances of producing cases of leptospirosis were reduced.

In the total of 333 cases, 20 were among officers. With few exceptions these were among the subaltern patrol-leading group and all were British: either in British infantry or serving with Africans or Fijians. No Malay officers (and there were plenty in this group) contracted the illness neither did any Gurkha officers.

Although cultural identifications when carried out showed a large number of different leptospiræ there seemed to be no fixed relationship between the causal leptospiræ and the severity of the illness. Cultural identification could not be done in all the cases but confirmation of the diagnosis by agglutination-lysis, complement fixation or a combination of both was the general rule. It is considered, however, that if it had been possible cultural isolation and identification on a wider scale would have helped to have given a clearer picture of the distribution of the various leptospiræ in Malaya. This might profitably be combined with more extensive serological studies among the indigenous population than has hitherto been possible. The relation of the various rodent hosts and the causal leptospira would also be of interest.

The experience of these two years has put the hazard of leptospirosis in Malaya into focus. From being underdiagnosed in the early stages it then passed through a small peak of overdiagnosis until now the picture is fairly clear. Cultural and serological methods are both essentials for a true picture. The varied clinical picture can cause confusion. This does not only apply to the disease as it is met in Malayan jungle. Admittedly the conditions it found there were optimum for its dispersal and such conditions on such a scale are unlikely to be encountered in ordinary existence. Nevertheless they can be encountered on a small scale from time to time. We must remember that Weil's disease is only one manifestation of the many that are possible in leptospirosis. To some extent we can prevent leptospirosis by adjusting environmental conditions so as to restrict the opportunities for the leptospiræ to reach the body. But conditions of warfare in the Malayan jungle with its ever-present reservoirs of infection and its abundant opportunity did not permit of such adjustments to be fully effective.

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Colonel A. P. Trimble:

Clinical Aspect of Leptospirosis in Malaya

This paper is the result of an analysis of the recorded observations in 236 cases of leptospirosis in Malaya over a period of four years. All were proved either by a rising agglutination titre or by blood culture. The only selection was the ready availability of the notes and the corresponding pathological results.

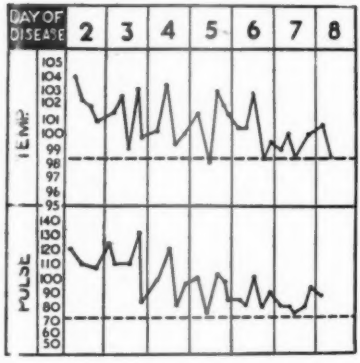
The disease as we have seen it corresponds in broad outline with the accepted textbook descriptions, i.e. it is a disease without prodromata, of abrupt febrile onset with nausea, vomiting and headache, usually associated early with body and limb pains and tenderness, and injected eyes. Towards the end of the first week in about four-fifths of the cases, renal (70%), hæmorrhagic (18%), hepatic (10%), or meningitic changes (3%) may be expected. Usually more than one occurs, occasionally all four, and the relative severity of each varies within wide limits. In Malaya it was commonly a moderately severe illness with pyrexia lasting a little over a week. It can be the cause of a short three-day fever; or it can be an overwhelming infection that is fatal in a few days. In Malaya dehydration in the early stages was an additional factor.

The signs and symptoms are listed in order of frequency in Table I. The temperature

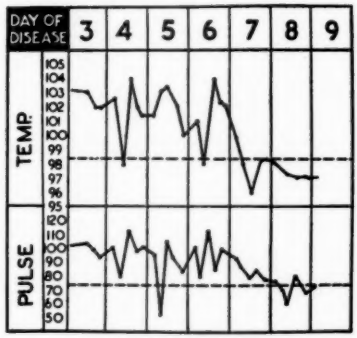
TABLE I.—ANALYSIS OF SYMPTOMS IN 236 CASES OF LEPTOSPIROSIS PROVED BY AGGLUTINATION AND/OR CULTURE ON FLETCHER'S MEDIUM

	%		%		%
Headache	98	Sore throat	25	Tender below L. costal margin	5
Conjunctival injection	80	Glandular enlargement	25	Abnormal C.S.F. found	3
Renal involvement (requiring gastric drip or I.V. glucose)	70 7	Rigors	18	No conjunctival injection or pain or tenderness in body or limbs	3
Vomiting	60	Bleeding	18	Total white count (extremes 4,000 to 30,000) averaged	9,000
Back and body pains	60	Rash present	16	Polymorphonuclear percentage (extremes 20% to 96%) averaged	75
Limb pains	60	Spleen palpable	15		
Muscle tenderness	50	Liver palpable	15		
Injected throat	45	Lumbar puncture performed	11		
Abdominal pain	35	Kernig's sign positive	10		
Neck stiffness	30	Icterus	10		
Cough	30	Tender below R. costal margin	10		
Physical signs in lungs	25				

is usually of the high remittent type. As in scrub typhus, a double rise and fall, perhaps to almost normal in the twenty-four hours, is frequent at some time of the disease. There is not infrequently some regression of symptoms after thirty-six hours but after a further twelve hours, the symptoms increase again and become more intense. The result is often a temperature chart with a distinctive high and very erratic outline and of value in diagnosis (Fig. 1). Rigors may occur. In three-quarters of this series the duration of



A.—Pte. E.



B.—Cpl. B.

FIG. 1A and B.—Two charts of leptospirosis cases to illustrate the high, erratic character of the pyrexia and the occurrence of a double rise and fall in the twenty-four hours.

pyrexia was seven to twelve days. There are three further points about the pyrexia. It not infrequently falls, sometimes to subnormal at the onset of severe renal involvement and may be accompanied here by a severe fall in blood pressure. The mild short secondary rise is well known. Very occasionally a low-grade intermittent pyrexia may follow the acute phase and continue for some weeks. There may be an injected throat (45%), and cough and signs in the chest (30 and 25%), with consolidation at the bases in severe cases. Although glandular enlargement was noted in 25%, the enlargement is very rarely prominent as is so frequently the case in scrub typhus. Although icterus occurred in only 10%, minor abnormalities in liver function tests were fairly common as occurs in many fevers.

Urinary changes.—In 30% of cases there were no urinary changes throughout or only an occasional trace of febrile albuminuria. Such absence of renal involvement is not confined to mild or moderately ill cases. For instance one severely ill patient with both meningitis and hæmatemesis showed no renal involvement throughout. Urinary changes are often delayed. However, even in patients where there has only been moderate urinary involvement there is often some impairment of dilution and concentration for some weeks. So far no case has shown persisting impairment for longer than three months. Warning of the onset of severe oliguria is always given by a study of the daily intake and output chart. In the early stages diminished urinary output and perhaps some rise in the blood urea were more often due to dehydration.

Meningitis.—The incidence of meningitis was only 3%. It was suspected in a further 8% but with normal findings on lumbar puncture. This does not support the contention that an appreciable number of cases have C.S.F. changes without meningeal signs. The fluid showed a moderate increase of cells (maximum 400), mainly lymphocytes, and a moderate increase of protein with low normal sugar levels.

Skin rashes.—There were macular or erythematous skin rashes in about one-fifth of the cases. They appeared on the chest and upper arms from day 2 to day 5. The face may be darkly suffused in the early stages. No hæmorrhagic herpes was noted but herpes labialis is uncommon in Malaya. One further rash occurred, mainly from one regiment during an outbreak. It consisted of macules very similar to rose spots appearing about the seventh day, first about the upper abdomen and spreading to the rest of the trunk and occasionally the limbs. It was associated with late urinary changes or none at all and sometimes an enlarged spleen.

Complications and relapses were few. The main complications were conjunctivitis and iritis. Others were thrombophlebitis, pyelitis and anæmia. Relapses were mild but resembled the original attack. Only two cases of second attacks were proved although the majority were exposed to further risks of infection.

Differential diagnosis.—In the first two days it is often quite impossible to diagnose leptospirosis clinically. At the end of a week it is possible to be correct in about 90% of cases. Points to remember in a typical moderate case are the rapid onset of a high erratic fever with severe headache, pains and vomiting. The eyes are injected, there may be subconjunctival hæmorrhages, and the face is often darkly suffused. The patient tends to lie on his back, immobile because of pain and prostration but he is mentally alert and the picture contrasts markedly with the typhoid state. Signs of involvement of other systems should be watched for, particularly daily examination of the urine. In Malaya, malaria and scrub typhus were the two most frequent difficulties. The prominence of nausea, vomiting and pains is suggestive but a tender spleen is relatively uncommon. On occasion the distinction is anything but clear. Scrub typhus is a very real difficulty and there are a number of cases where it is impossible to differentiate on clinical grounds. Enlarged and tender glands are much more frequent in scrub typhus. It should be noted that the initial OXK titre in the Wilson-Weil-Felix reaction can be high in leptospirosis, but it subsequently falls. Chloromycetin may be used diagnostically. Other difficulties are atypical dengue, the undifferentiated P.U.O.(S.T.) of the tropics, pyelitis and infective hepatitis with hepato-renal syndrome. A polymorphonuclear leucocytosis is almost constant in leptospirosis, and this may help the diagnosis.

Relation of sero-types to severity and symptoms.—I was interested to see if this series supported the claim that different sero-types produced clinically different syndromes (Table II). The overall picture is that leptospirosis most commonly produces a moderately severe illness (the average time off duty was four weeks). Less frequently it produces either a severe or a mild illness in almost equal proportions. None of the groups is markedly different from its fellow, taking chance into account. Certainly icterohæmorrhagiæ, the classically severe sero-type, does not stand out as such. With regard to symptoms, renal involvement is roughly in the same proportion throughout, and analysis of its severity was also proportional. The same observation applies to the frequency of

TABLE II.—RELATION OF SERO-TYPES TO SEVERITY AND SYMPTOMS

	Total	Severe	Moderate	Mild	Renal signs	Icteric	Hæmorrhagic signs	Rash	C.S.F. changes
?*L. icterohæmorrhagiæ* ?*L. canicola*	38	1	29	8	23	nil	6	8	2
L. icterohæmorrhagiæ	28	2	21	5	18	5	4	8	nil
L. bataviæ	17	3	11	3	14	2	3	3	nil
L. autumnalis or *autumnalis* group	17	1	11	5	14	2	4	3	nil
L. canicola	15	3	8	4	7	nil	2	2	nil
L. hebdomadis	14	2	11	1	11	nil	1	3	nil
L. medanensis	6	nil	5	1	5	nil	1	2	nil
L. grippotyphosa	6	2	3	1	4	nil	2	1	nil
L. rachmat	5	2	2	1	5	1	1	nil	nil
L. pyrogenes	5	nil	2	3	4	nil	nil	nil	nil
?*L. benjamini* ?*L. schüffneri* ..	4	2	2	nil	4	nil	nil	1	nil
L. wolffii	3	2	1	nil	3	nil	1	nil	nil
L. celledoni	3	1	1	1	1	nil	1	nil	3
L. bangkinang	2	1	nil	1	2	1	2	1	nil
L. poi	1	nil	1	nil	1	nil	nil	nil	nil
L. australis B	1	nil	nil	1	1	1	nil	nil	nil
Unidentified or anomalous ..	71	12	53	6	50	9	13	5	1
Total	236	34	161	41	167	21	41	37	6

Unidentified or anomalous = either culture positive but identification of organism not proceeded with or an equal rise of agglutination titres in more than one sero-type.

hæmorrhagic signs. Icterus did not occur in any of the so-called non-icteric strains, but neither icterus nor hæmorrhagic signs were particularly frequent in icterohæmorrhagiæ. In any case icterus has on occasion been reported in some of the non-icteric types, e.g. canicola and grippotyphosa. Canicola is reputed to cause meningitis frequently. There was no occurrence in our 15 cases. But this is not to claim that there is no correlation. For instance the rose-spot type of rash mentioned before appeared to be associated with either *L. icterohæmorrhagiæ*, *L. canicola* or (more frequently) that anomalous group which showed the serological features of both. The analysis does not support any very close correlation with either severity or individual symptoms.

Summary.—I would suggest that in the past there has been too great a tendency to categorize this disease into a number of clear-cut clinical types often allegedly associated with specific sero-types. It is a disease of extreme variability in severity and of a wide symptomatology, the clinical types overlap in a multitude of ways and the disease is better described as a whole. Study of van Thiel's monograph supports this contention.

Fatal cases.—It may be of interest to describe 8 fatal cases diagnosed as leptospirosis. Although only one was pathologically proved by culture, the diagnosis in the others was clinically satisfactory. All were jaundiced but only 4 heavily so. In nearly all there was a marked hæmorrhagic tendency. 3 patients (one of whom was proved culturally) appeared to die of overwhelming septicæmia on days 4, 5 and 6 respectively. Post-mortem revealed a widespread hæmorrhagic pneumonia with only minor changes in liver and kidneys. Two cases dying on days 7 and 9 were considered to die of liver failure, being deeply jaundiced with reasonable urinary output. Restlessness, delirum and finally coma occurred. The 3 other patients appeared to die of renal failure on days 10, 11, and 14. There would thus appear to be three distinct forms of death—septicæmic, hepatic and renal.

Treatment is initially concerned with the correction of dehydration and the relief of pain and nausea. Pethedine is a most valuable drug. Daily intake and output charts give warning of impending renal failure which can usually be treated adequately by the Borst and Bull regime. It is important to distinguish between the oliguria due to uncorrected dehydration and that due to the disease. If gastric drip cannot be tolerated, or hepatic failure supervenes, inferior vena caval transfusion with 40% glucose should be carried out. The restlessness of hepatic failure will need paraldehyde. Meningitic symptoms are quickly relieved by lumbar puncture. I have no doubt that it is the modern treatment of dehydration and of renal failure that has produced the very low mortality rate (under 2%) in the Army in Malaya. There has been sharp difference of opinion over the value of antibiotics.

Smadel was unconvinced that any of the current antibiotics was effective but favourable claims for penicillin have been made in this country. I have emphasized the great variability in severity and therefore no true assessment can be made except in carefully controlled and reasonably large series. Such assessment must be made on the total symptomatology, and not, for instance, on duration of pyrexia alone. Such a series was reported by Fairburn and Semple and failed to show marked improvement with either penicillin or Chloromycetin. Oral Aureomycin is too irritating. A controlled series with terramycin is at present being carried out. My own opinion is that there is some advantage if antibiotics are given very early in the disease but it is extremely difficult to admit, diagnose and start specific treatment of cases of leptospirosis within forty-eight hours of onset without haphazardly treating a number of quite unrelated diseases. Certainly we have as yet no true specific therapy such as we have for typhoid fever and scrub typhus.

Finally, it has been alleged that leptospirosis in Malaya is one of the milder variants. This analysis does not support that claim (*see* Table II). The number of mild cases is more probably due to the exceptional hospital and laboratory facilities available. There are a large number of sero-types present in Malaya and here they were acting on a completely non-immune community. It is therefore reasonable to suppose that the disease as we see it there is a true reflection of the natural history.

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Section of Physical Medicine

President—A. C. BOYLE, M.D., M.R.C.P.

[*December* 12, 1956]

DISCUSSION ON REHABILITATION IN THE ROYAL AIR FORCE

Sir Reginald Watson-Jones:

In former years immobilization of fractures was accompanied by such grave disuse change, with stiffness of joints and wasting of muscles, that Lucas-Championnière went to the length of treating fractures without any immobilization at all. Even until recent years some surgeons have been so afraid of the effects of immobility that they have been ready to discard the use of any form of splints or plaster. The fact is, of course, that a fractured bone or injured joint can be immobilized quite safely without danger of permanent stiffness or muscle wasting provided that throughout the period of immobility the patient is instructed in exercises of the distal joints and static contraction of the muscles in the immobilized area. This applies whether it is a fractured leg in an above-knee plaster, a fractured femur in a Thomas's splint, a fractured spine in a plaster jacket, a fractured wrist in a below-elbow plaster, or a fractured elbow or humerus in an above-elbow plaster. The essential treatment, apart from reduction of the displacement of bones, is to teach the patient active exercises and to make certain that he carries them out regularly at hourly intervals throughout the day for about five minutes each time. It is equally important when splints or plasters have been discarded to teach active exercises by which to regain mobility of joints, always encouraging, cajoling, and persuading the patient to do them hourly throughout every day until functional recovery is complete.

During the First World War Sir Robert Jones planned remedial workshops for this stage of rehabilitation. The centre at Roehampton deservedly gained wide repute. The demands of war have always stimulated the advance of medicine and surgery: as for example the development of nursing under the direction of Florence Nightingale in the Crimean War; the control of disease and treatment of wounds by Ambroïse Paré; the development of antisepsis and asepsis by Pasteur and Lister; the development of antibiotics by Fleming and Florey; the progress of anæsthesia in Edinburgh and Boston; and advancement of the treatment of bone injuries by Hugh Owen Thomas, Robert Jones, and many of their disciples.

Early in the Second World War the importance of gaining complete and rapid recovery from the injuries sustained by pilots, air crews, and ground staff of the Royal Air Force was so great that early active exercises in the hospital wards by rehabilitation orderlies, and follow-up treatment with gymnasia, recreation grounds, and swimming pools in special rehabilitation centres was soon established. It was my opportunity and great privilege, with the enthusiasm of the Director-General of the medical services and the Consultants in Physical Medicine of the Royal Air Force to establish these centres. Fortunately the lesson was not forgotten immediately after the conclusion of the recent great war, and the Royal Air Force medical services still have most excellent rehabilitation centres—the magnificent centre at Headley Court being provided entirely by voluntary subscription. This important development in the management of patients with severe, serious, and often multiple fractures—including for example ten, twenty, or thirty fractures sustained by one pilot—was soon emulated by the Army, the Royal Navy, the U.S. Army, the Australian Forces and the Canadian Forces, and the impetus thus gained has been sustained.

It must be emphasized that the principle of rehabilitation is to encourage and persuade the patient to cure himself. This principle was declared nearly two thousand years ago by Galen who said: "He cures most in whom most are confident"; and even earlier by Plato who said: "This is the greatest error in the treatment of sickness, that there are physicians for the body and physicians for the soul, and yet the two are one and indivisible." The principle of rehabilitation, whether in the earlier stages in hospital wards or the later treatment in special rehabilitation centres, is to encourage active exercises with no passive measures of stretching, forcing, and manipulating, and at the same time to let the patient understand his disability, regain confidence and be inspired, always making sure that fears and anxieties are dispelled, and that social problems are solved. Physical exercise alone is not rehabilitation; psychological and social treatment is just as important as active physical treatment.

Dr. Basil Kiernander:

An extremely happy relationship has developed between the specialties of orthopædic surgery and physical medicine and has enabled the organization to work very efficiently in an atmosphere of unity. This was largely due to the personality of the consultants in Ortho-

pædics, Sir Reginald Watson-Jones and Mr. H. Osmond-Clarke on the one hand, and of the consultants in Physical Medicine, Sir Morton Smart and Dr. C. B. Heald, on the other. The R.A.F. was fortunate in having so many pioneer Medical Officers employed in the specialty of rehabilitation and physical medicine. In this connexion I would comment on the liaison in the R.A.F. between the physical fitness officers and the physical medicine specialists, by which they co-operate not only in the training and provision of suitably qualified physical training instructors in rehabilitation centres and hospitals, but also in the preventive field in which I am particularly interested.

In addition to staffing the residential rehabilitation centres, the physical medicine specialists of the R.A.F. have to supervise the physical medicine departments of R.A.F. hospitals as well as that of the Central Medical Establishment in London. The field in the rehabilitation centres is still largely orthopædic, although other types of cases are being encouraged, e.g. up to 5% psychiatric. At the physical medicine departments there is a cross-section of all types of disorders—medical, surgical, gynæcological and psychiatric—and this is comparable with the experience in a civilian hospital, except that the majority of patients are in the younger age groups. In addition to Service personnel the wives and families of regular members of the R.A.F. are looked after medically, and this introduces a broader sphere of clinical experience than would be possible otherwise. Ideally the rehabilitation centres should eventually be situated within easy reach of the hospitals they serve, as while the atmosphere will then be the correct one of recovery the patients will be capable of transfer there from hospital at an earlier date than at present, when a long distance may have to be travelled. Hence, in addition to speeding recovery and freeing the more expensive hospital bed, it will enable the clinical staff of the hospital to visit the patients in the rehabilitation centres and assess their progress.

To-day the residential rehabilitation centres in the R.A.F. are staffed medically by specialists and trainee-specialists in physical medicine under the administrative control of a medical commanding officer. These officers have full clinical control of the patients during their stay in the centres. They also keep in close touch with the clinicians referring them. They supervise both the physical and mental rehabilitation of the patients, and where necessary vocational training and resettlement in civilian life. Regular visits are made by the R.A.F. orthopædic and other specialists to review their cases, and occasional visits are made as required by Mr. Osmond-Clarke, the Consultant in Orthopædics, and myself.

The importance of early treatment for those patients suitable for admission to the residential rehabilitation centres has been stressed by Sir Reginald Watson-Jones as a method of cutting down periods off duty after hospitalization and reducing sick leave, from which the patients so often return no better. There are an even larger number of patients who have minor disabilities which do not necessitate admission to the residential rehabilitation centres but who can be kept on duty and helped considerably in their return to normality by correct physiotherapy based on active exercises as out-patients, these treatments being carried out strictly by appointment to prevent wastage of man-power time.

The physical medicine department of the R.A.F. Central Medical Establishment offers an example of the need for this type of department.

It was established in 1942, in the first instance primarily for the treatment of minor injuries and postural defects of the several thousand air crew cadets at that time stationed in London, but shortly afterwards it expanded to provide a complete diagnostic and therapeutic physical medicine centre for out-patients stationed in London or within easy reach thereof. By the early summer of 1944 this department had so expanded that a large house in Regent's Park was converted to meet its needs. At that time it was in my charge with the help of the late Sir Morton Smart as Honorary Consultant in Physical Medicine, and in addition to the administrative staff we had ten physiotherapists and an X-ray Department with its own radiographer. This department was able to deal with some 30 new patients a day referred for an opinion, and on the therapeutic side of carrying out treatment for some 7,000 patients per annum. The department suffered repeated damage from enemy action but the work never stopped, and morale was boosted by visits from Their Majesties the King and Queen and other members of the Royal Family during this period. Many of the acute minor disabilities of the locomotor system were dealt with here and the department, although smaller to deal with the needs of the peacetime R.A.F., still continues as a diagnostic and therapeutic centre in the Central Medical Establishment to-day.

A number of interesting surveys and pieces of original research have been done in this department, including on the diagnostic side the use of the first electromyograph employed in the R.A.F.; and a study of various methods of dealing with minor injuries was made, varying from the wartime use of ethyl chloride sprays to the local injection of hydrocortisone at a later date, followed in both cases by early mobilization. A wide variety of pathological conditions were dealt with, including a number of peripheral nerve lesions produced as the result of enemy action, injury from air or other accidents. It is interesting that the first group of patients with poliomyelitis in minor form following serum injections was met with at this Centre during the war. Since the war other research projects have continued and a

the present time, and indeed for the last seven years, a survey of all the cases of facial palsy in the R.A.F. has been studied with the help of the E.N.T. and neurological specialists.

In the post-war period the training of physical medicine specialists and physiotherapists has continued. The R.A.F. is a recognized training centre for the Diploma in Physical Medicine of the Royal College of Surgeons and Royal College of Physicians, the training being provided at the rehabilitation centres and the physical medicine department of the Central Medical Establishment. Where possible, the trainee specialists are also given experience at outside teaching hospitals. Sixteen out of the ninety-five holders of the D.Phys.Med. have received their basic experience and training in the R.A.F., and of these a number have obtained consultant posts in civilian life while a basic core of physical medicine specialists is maintained in the regular R.A.F. Medical Service. The training has proved of such value that the R.C.A.F. have now sent over two regular medical officers for two years' training in this subject.

The R.A.F. now has a physiotherapy training school recognized by the Chartered Society of Physiotherapists for their diploma. The new school was opened last month at R.A.F. Hospital, Halton, and the Medical Rehabilitation Centre at Chessington, with opportunities of obtaining additional experience in appropriate civilian hospitals. In the near future a training school for remedial gymnasts is being opened in the R.A.F. also.

In addition to their work in these various spheres, the medical officers engaged in the specialty are encouraged to carry out research and to take an active part in the appropriate civilian specialist organizations such as this Section and the British Association of Physical Medicine, and to give their services to civilian committees, including working parties of the Ministry of Health and committees set up by the Medical Research Council.

Squadron Leader P. J. R. Nichols:

The R.A.F. Rehabilitation Units at Collaton Cross in Devon and Chessington in Surrey have been functioning continuously since 1946, and up to December 1955 have treated over 26,000 patients, and it is upon the results of treatment at Chessington and Collaton Cross between 1952 and 1955 that this paper is based.

Fractures of the shaft of the tibia.—A total of 353 cases have been studied; 249 patients were treated by closed reduction, including 33 with compound fractures. The 104 patients treated with open reduction included those with internal immobilization with Küntscher nails, screws, plates and bone grafts. The time for clinical union in this series is directly comparable to that recorded by Watson-Jones and Coltart in 1943 (Tables I and II).

TABLE I.—TIME FOR CLINICAL UNION FOR FRACTURES OF SHAFT OF TIBIA AND FIBULA

Weeks for union	Present series	Watson-Jones and Coltart
Under 12	88 (22·1%)	99 (23·7%)
12–24	192 (54·4%)	224 (53·7%)
Over 24	73 (23·5%)	94 (22·6%)

TABLE II.—RESULTS OF REHABILITATION AFTER FRACTURES OF SHAFT OF TIBIA AND FIBULA

	No. of patients	Returned to duty	Regaining "Good" ankle range	Regaining "Good" knee range	Average Total Disability period
Closed Reduction					
Simple fractures ..	216	95%	95%	99%	25 weeks
Compound fractures	33	91%	99·5%	100%	30 weeks
Open Reduction ..	104	92%	97%	96%	35 weeks
Total	353	94%	95·75%	98·3%	28 weeks

Factors affecting the rehabilitation time.—The period between the clinical union of the fracture and return to duty has been termed "rehabilitation time" irrespective of whether the time was spent wholly or only partly at a rehabilitation unit.

214 patients were admitted at least four weeks before clinical union of the fracture of the tibia; the average rehabilitation time was eight weeks, whereas the average rehabilitation time for the 91 patients admitted after clinical union was twelve and a half weeks. The rehabilitation time is very variable and depends on many factors, anatomical, temperamental, and upon the duty for which the patient must be prepared. However, there are three clear trends:

(*a*) The slower the rate of union, the slightly longer the period of rehabilitation required;

(*b*) Open reduction prolongs rehabilitation time.

(*c*) The earlier the transfer of patients to the rehabilitation unit before clinical union, the shorter the "rehabilitation time" (Table III).

TABLE III.—EFFECT OF TRANSFER TO M.R.U. BEFORE OR AFTER CLINICAL UNION (CASES TREATED BY TRACTION EXCLUDED) ON TIME TAKEN FOR REHABILITATION

	No. of patients	Average "rehabilitation time" in days
Closed Reduction		
Simple Fractures		
Admitted before clinical union	134	43
Admitted after clinical union	62	78
Compound Fractures		
Admitted before clinical union	24	67
Admitted after clinical union	7	106
Open Reduction (plates or screws only)		
Admitted before clinical union	56	66
Admitted after clinical union	22	114
All Cases		
Admitted before clinical union	214	58
Admitted after clinical union	91	88
Total	305	67

Fractures of the shaft of the femur.—Fractures of the femur present greater individual problems in treatment and are thus more difficult to analyse in this type of survey (even when the study is confined to fractures of the shaft), as the management of these patients differs much from surgeon to surgeon and from case to case.

80% of our patients with fractures of the shaft of the femur returned to duty, and 80% of these patients regained 90 degrees knee bend or more (Table IV).

TABLE IV.—COMPARISON OF RESULTS OF REHABILITATION AFTER FRACTURES OF THE SHAFT OF THE FEMUR

Type of treatment	No. of patients	No. returned to duty	No. regaining 90 degrees or more flexion of knee	Average time of total disability from injury or from operation
Delayed intramedullary nailing ..	16	13 (81%)	13 (81%)	277 days
Non-skeletal traction	25	18 (72%)	17 (68%)	261 ,,
Open reduction and plating	11	7 (64%)	8 (72%)	258 ,,
Skeletal traction	17	16 (95%)	16 (95%)	253 ,,
Immediate intramedullary nailing ..	24	20 (84%)	23 (96%)	177 ,,
Total	93	74 (79·5%)	77 (83%)	240 days

Although there are so many more variables than in the case of fracture of the tibial shaft, a simple analysis does show a trend indicating that early transfer to rehabilitation units tends to shorten the rehabilitation time (*see* Table VII).

Fractures of the head of the radius.—Fractures of the head of the radius constitute 5% of all fractures (Murray, 1940). Most cases are treated conservatively with two or three weeks' immobilization followed by graduated mobilization. Comminuted fractures and those with marked displacement are frequently treated by excision of head or of the fragment.

53 cases from Collaton Cross and Chessington are available for detailed analysis in two groups: (*a*) those patients with undisplaced fractures treated conservatively; (*b*) those treated by total excision (Table V).

TABLE V.—COMPARISON OF RESULTS OF REHABILITATION AFTER FRACTURE OF HEAD OF RADIUS

Treatment	No. of cases	Average rehab. time in days	Average total disability period in days	No. gaining full extension	No. gaining full flexion	No. gaining full pronation	No. gaining full supination
Conservative	27	31	57	17 (71%)	21 (77·5%)	24 (89%)	26 (96·5%)
Total excision of head	26	63	69	11 (47·5%)	18 (69%)	20 (76·5%)	15 (51·5%)

Our results are compared with figures calculated from the review by Murray (1940) of 459 cases with an average of two and a half years' follow-up. In the case of closed reduction the present series gives immediate results as good as those of Murray's at follow-up, and in the case of total excision of the head the results are better and with a shorter disability period (Table VI).

TABLE VI.—COMPARISON OF PRESENT SERIES WITH RESULTS CALCULATED FROM MURRAY (1940)

Treatment	% of patients obtaining full movements or with less than 10 degrees of limitation		Average disability period (in weeks)	
	Present series	Murray's series	Present series	Murray's series
Conservative	80%	82%	8	5½
Total excision of head ..	70%	44%	10	18

More detailed analysis emphasizes once again the value of early transfer to the rehabilitation unit.

SUMMARY AND CONCLUSIONS

This survey of three disabilities treated at Royal Air Force medical rehabilitation units has, in effect, been a study of the rehabilitation of three joints, and three completely different sets of circumstances and problems of rehabilitation.

Table VII shows the saving of time by early transfer to the full-time Medical Rehabilitation Units in the three disabilities under discussion.

TABLE VII.—SAVING OF TIME IN THE TOTAL DISABILITY PERIOD BY EARLY TRANSFER OF PATIENTS TO REHABILITATION UNITS

Disability	No. of patients	Average total disability period (days) from injury or operation	Average time saved by early transfer (days)	% of total disability period saved by early transfer
Fractured Shaft of Tibia				
Closed reduction (simple fractures)	196	176	35	20%
Closed reduction (compound fractures)	31	212	39	18%
Open reduction	78	223	48	22%
Fractured Shaft of Femur				
Traction	42	258	25	10%
Intramedullary nailing ..	40	203	32	16%
Fractured Head of Radius				
Closed reduction	24	53	23	43%
Total excision	26	69	17	25%

It is most important not to become too obsessed by speed of recovery and the times involved, for, as Holdsworth (1942) stated, as quoted by Watson-Jones and Coltart (1943), "The test of success in the treatment of a fracture is the quality of end-result rather than the time taken in achieving the end-result".

In our organization the determining factor in the disposal of the patient is his functional capability. Within certain limits patients are retained until optimum recovery has been made. Thus variations in treatment are reflected in the time taken to gain specified functional results rather than in variations in end-results, and thus comparisons must be mainly related to the time factor.

What are the alternatives to full-time rehabilitation?

Patients could be retained in hospital; economically a poor solution for the overheads of hospitals are considerably greater than those of rehabilitation units. The patients may be sent on prolonged sick leave to be cosseted at home and allow their muscles to waste and joints to stiffen, to be treated like invalids and lose their morale. Or thirdly they may be given out-patient treatment; but there is no comparison between two or three sessions a week in a hospital out-patient department with the five-hours-a-day programme of residential rehabilitation in an atmosphere of recovery.

We believe that full-time rehabilitation gives results which are superior subjectively and objectively to those obtained by any of the alternatives, and therefore should be more widely available.

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Squadron Leader J. L. Milligan:

At Royal Air Force medical rehabilitation units weekly resettlement clinics are held for patients who are to be invalided. Here their future employment is discussed and where possible a trial of work is undertaken, either on the unit or under the auspices of G.T.C. Waddon. In these ways a patient may see for himself his suitability for the particular work.

A co-ordination visit to the local disablement resettlement officer is then undertaken to ascertain local employment facilities in the desired work. In this way it is possible for a man to go straight into a job of work or a G.T.C. at invaliding.

The measure of success of this scheme may be seen in the results of a follow-up which has been made over the last five years.

257 replies have been received in answer to a standard *pro forma*. The follow-up period after invaliding varies from a few months to four years, the majority are between eighteen months to two years. 196 or 76% thought the clinic had been of help to them, 34 or 13·2% were not helped. 9 did not need the help of the clinic and 18 gave no reply. The above figure of 76% is probably low because it was obvious from some replies that the resettlement clinic was not differentiated from rehabilitation as a whole.

67 or nearly 26% undertook government training courses and a further 16 undertook various types of private training. Only 3 of the government trainees were dissatisfied with the training they received; the complaints were of out-of-date methods or equipment. A more detailed survey of patients who have had government training courses has recently been undertaken. Allowances were agreed to be just about adequate, but many prospective candidates who were married have been put off courses because of the inadequacy of allowances. Most trainees pointed out the necessity of finding out the local prospects in their trade before undergoing a course.

Three trainees did not subsequently take up the trade of their training, but all said that the courses gave them confidence and independence and were consequently valuable experiences. All but one were registered disabled persons and they found no snags in dealing with their employers on this account. The majority stated that they were better off as a result of their training than they were before entering the R.A.F. or before their disability.

211 or 83% had no difficulty in finding a job on leaving the unit or training centre. 33 had some difficulty, mostly the more severely disabled. 9 were not in work because of their disability and only one is in a home for the permanently disabled.

Of the 244 patients in employment, 193 or 76% were in the same employment as on their discharge. The remainder have changed their employment at least once, of these some were of a temporary nature while awaiting a training course.

205 or 81% were happy about their job and its prospects, of the rest 18 had trouble because of a recurrent disability, 11 were not in the work of their choice often because of their disability and 10 gave no reason for their dissatisfaction.

Of their disability, 121 said it remained static, 95 that it was better and 31 that it was worse. In 4 the condition was stated to be variable.

Our main interest lay in the causes for 33 failures, that is to say with those who had difficulty in finding work, with a view to eliminating these in the future. Of the 33, 11 had difficulty because of chronic relapsing disabilities. These still form the hard core of resettlement problems and no complete answer has yet been found. Two patients were in districts where there was little variety of employment, one a severe poliomyelitis of the (R) arm was forced to do labouring, there being no local alternative, and he is now unemployed. The remainder was due to insufficient adjustment to a disability. It is difficult to see how human error can be completely eliminated in these cases, although increased experience helps.

Many patients remarked on the inadequacy of local D.R.O. facilities, especially following the excellent co-operation and the well-informed nature of the disablement resettlement officers who attend the resettlement clinics. This difficulty has been remarked upon with reference to the training for disablement resettlement officers in the Piercy Report. In an earlier report we quoted that employers were anti-disabled and uninformed, but the more recent replies show that this outlook is decreasing. Only one man stated that his employer was unwilling to pay him full wages for full work simply because he was disabled. Equality for the disabled must still occasionally be the cry. It is obvious from some replies that the liaison between doctor, disablement resettlement officer and employer is still not as good as it should be; surely the medical profession should lead the way.

In all cases the mainstay of the resettlement clinic's success must be the thorough understanding of the patient, his disability and his family background, and no one is in a better position to undertake this than the doctor in charge of the patient. This responsibility we try to accept at R.A.F. medical rehabilitation units, and I trust that we shall continue to try to improve our successes from 86% to 100%.

Squadron Leader C. B. Wynn Parry:

The special features of a rehabilitation centre are the ability to give a full day's really intensive treatment in an atmosphere of confidence and optimism. It is an advantage to have patients with similar disabilities working together, particularly if they can up to a point vie with each other in their speed of recovery and draw heart from seeing others with like afflictions progressing well. The severer the injury and degree of complications, the more likely is a better functional result with full-time treatment.

As an example of this I would like to quote the case of a patient who was involved in a motor cycle accident in July 1955, sustaining a fracture of the left femur and a fracture of the left tibia and

fibula. He also sustained a traction lesion of the sciatic nerve. Five months after injury he was transferred from hospital to the centre for full-time rehabilitation. It was decided that he would need amputation below the knee because of the non-union of the tibial fracture and the complete nerve lesion. Electromyography, however, about five months later showed that there were some early regenerative potentials in the calf muscle and also in the anterior tibials. Treatment was intensified involving non-weight-bearing exercises with knee bend and ankle movements, stimulation of the denervated muscles and re-education of the recovering muscles. To-day the regeneration is such that he has good function in the calf muscle and is now beginning to dorsiflex his toes and ankle. He has knee movements of 175–115 degrees. The skin condition is now very good and there is no doubt that he will keep his leg. Apart from the obvious benefit of the rehabilitation centre in allowing intensive treatment, despite inability of the patient to weight-bear, the effect on his morale has been immeasurable. In a centre of this sort he sees other patients similarly afflicted and has such a full day's programme with discussion groups, entertainments, &c., in the evening that he has very little time to be introspective. Despite his severe disability he has become highly independent, which is after all one of the important aims of treatment at these centres. It is doubtful if the patient's physical and mental condition would have been so good had he not been in a residential centre.

Severely handicapped patients with poliomyelitis, disseminated sclerosis, hemiplegia, paraplegia, and other neurological disorders require retraining in walking, climbing stairs, dressing, shaving and other toilet activities, individual and group muscle re-education, functional assessment for work and vocational training.

Such a patient needs the whole range of a rehabilitation centre's facilities—physiotherapy, occupational therapy, hydrotherapy, educational, welfare and retraining. Not only are these manifold aspects of the patient's recovery difficult if not impossible to cater for in a hospital but the day-to-day observation of progress which is so vital to successful rehabilitation and resettlement is out of the question. The atmosphere engendered by a team approach and the detailed attention to myriad small points in treatment and retraining which make so much difference to the patient's life are not easily given except in a special centre.

The facilities of a rehabilitation centre are no better exploited than in the treatment of severe hand injuries, a subject which is somewhat neglected as a whole but is one of obvious importance. Some illustrative cases follow:

Patient F. J. put his right hand through a window while sleepwalking in June 1955 and severed all the structures in front of the wrist.

Eight days later secondary suture of all the tendons and the median and ulnar nerves was performed. One month later he was admitted to the rehabilitation centre. On arrival he presented with a virtually solid wrist held at 30 degrees palmar flexion, no movements in the m.p. joints, a dry scaly completely anæsthetic hand, very œdematous and an unhealed wound. The patient was a motor fitter, this was his right hand and so the best possible function was essential.

One month after starting rehabilitation he had regained 15 degrees wrist movements but the wrist scar was thick and firmly adherent. The arm was held in elevation, in a sling to counteract the œdema for the first month. Active exercises, electrical stimulation, light craft work and four sessions of oil massage to the scar made up a very full day.

At two months after nerve suture, stretching began in earnest.

In our experience the type of stiff wrist and fingers due to severe lesions such as these with gross tendon adherence at the wrist and resulting flexion deformities of the fingers do not improve with simple active exercises and normal use alone, some form of passive therapy is essential. Manipulations are, of course, completely contra-indicated as they produce more damage and deformity than before. Long-continued slow stretch is the treatment of choice for this type of stiffness.

In the early stages, a plaster splint is moulded on to the patient's hand, being applied from just below the elbow to beyond the finger tips on the palmar surface. The splint is applied immediately after maximum passive correction of the deformity and worn during the day when not undergoing treatment and at night. These splints are changed twice a day in the first two to three weeks, then daily, then every other day and eventually once a week, at this stage the splint only being worn at night. The whole aim of this intensive stretch is to retain every degree of increased movement won in the treatment sessions.

After six weeks' treatment there was 45 degrees palmar flexion and 10 degrees dorsiflexion, a full passive range of the i.p. joints when the m.p. joints were flexed but a 70 degree deformity in m.p. extension.

By three months, a full range of wrist movements was restored and there was only a 10 degree flexion deformity of the i.p. joint. The scarring and adherence were almost gone and the hand was looking in good condition. Lively splints were made to prevent deformity and encourage function in the workshops and in normal use (Smythe and Wynn Parry, 1955). The nerves recovered at the rate expected of neurontmesis and a full programme of re-education started. This included two half-hour sessions of individual muscle exercise, and pattern re-education in the physiotherapy department, a wide variety of games and craftwork in the occupational therapy department, such as basketry, leatherwork, and carpentry. Metal work and job re-education came later when sensation and functional recovery allowed. In all, he spent nine months at the Unit and when discharged was able to undertake all the duties of his trade as motor fitter.

On review fifteen months after injury, his sensation was almost completely normal, all muscles

except third and fourth interossei were working well. His grip was 1 lb. less than the other hand and the only things he could not manage with ease were very fine manœuvres such as putting a split pin into a hole, but this was improving all the time.

There are a number of features in this type of case that deserve comment. The gross adherence and stiffness and flexion deformities that inevitably arise in a severe lesion require full-time very carefully graded intensive attention, the recovery of power and fine function necessitates extensive re-education.

Such patients need constant encouragement best afforded by a centre where others with the same disability are being treated. It must be stressed that the best results in our experience demand really detailed and closely supervised therapy. Choice of work activities in the various stages of recovery must be carefully matched against what muscle action is present and sensory hyperæsthesia. It is no good expecting a man to handle a screwdriver if it causes unpleasant hyperæsthesia throughout the hand, as commonly happens in recovering nerve lesions. With very few exceptions these patients never regain good function if sent back to work in the hope that they will rehabilitate themselves. These patients require full-time intensive rehabilitation for months on end.

The second example of a hand injury I would like to give is that of a patient who sustained extensive burns of the hand in an aircraft crash as well as to face, legs and shoulders. Skin grafting was carried out five and twelve days later and he came to the centre 2/12 after the accident. The backs of both hands were covered in thick tough scars, such that there was no flexion in the fingers and 10 degrees palmar flexion only (Fig. 1). A full programme of oil massage several times a day,



FIG. 1.—Maximum range of flexion of fingers two months after burns.



FIG. 2.—Range of flexion after seven months' treatment. → Same case as Fig. 1.

O.T. exercises, active assisted movements was carried out. During the course of treatment he twice returned to hospital for excision of scars and webs with thin split grafts.

9/12 after the accident he had virtually normal hands and was able to return to full duty (Fig. 2).

It has been my purpose to suggest that for a certain type of patient, a full-time intensive regime of treatment in a special centre offers the best opportunity for the best functional results. Whether a day or residential centre is best or fuller use of hospital facilities depends so much on the district, work available, patient's domestic background and many other factors. But the choice is unimportant compared with the principle of the service offered.

It is our opinion that for patients who would materially benefit from such treatment, more centres should be established. Perhaps local industry might make work available to these centres so that patients undergoing rehabilitation might earn by productive work arranged where possible to increase function of the particular limb, on the lines pioneered by Vauxhalls.

There would be immense practical difficulties in such a scheme but as people will continue to suffer from locomotor disorders, ride motor cycles and put their hands through windows it might be worth making a start.

ACKNOWLEDGMENTS

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JOINT MEETING No. 1

Section of Orthopædics with Section of Physical Medicine

Chairman—E. STANLEY EVANS, C.B.E., F.R.C.S.
(President of the Section of Orthopædics)

[*October* 18, 1956]

DISCUSSION ON THE PRESENT POSITION OF MANIPULATIVE TREATMENT

Sir Reginald Watson-Jones: It is intended that this discussion should exclude such manipulative treatment as is concerned with the reduction of dislocations and displaced fractures, and that it should be limited to other types of manipulative treatment. There are five groups of cases to be considered: (1) Mobilization by manipulation of joints seriously stiff after injury or prolonged immobilization in plaster; (2) joints with minor strain in which manipulation may be needed for local adhesion formation; (3) osteoarthritic joints in which symptoms may sometimes be relieved by manipulation and stretching of the associated adhesions; (4) manipulations of joints of the spine for adhesions or prolapse of intervertebral discs; (5) minor manipulation which is to be regarded as part of the psychological treatment of a patient with a functional disorder superimposed on minor physical disability.

(1) *Manipulation of seriously stiff joints.*—For at least fifty years it has been known that joints seriously stiff with massive adhesion formation react badly to manipulation under anæsthesia, and still more badly to repeated manipulation day by day. Although it is true that such manipulations stretch or tear adhesions the sero-fibrinous exudate of the manipulation gives rise to still more stiffness. This is shown most clearly when the metacarpo-phalangeal and interphalangeal joints of the fingers are stiff after injuries of the hand and wrist. The greater the force that is applied the greater is the stiffness of the joints. The essential treatment in these cases is the patient's active exercises repeated hourly throughout the day with no more passive aid than by the patient himself and certainly not by forcible stretching by a physiotherapist or forcible manipulation under anæsthesia by a surgeon. Physiotherapists at their meetings always deny that such forcible measures are used, but in fact they are, even up to this very day. Hardly a week goes by without me seeing a patient with stiff fingers whose joints are being made still more stiff by such measures.

The same is quite obviously true of the injured elbow. Ordinarily a supracondylar fracture of the humerus, or fracture of the head of the radius, or even simple traumatic synovitis will always regain a normal range of movement if the joint is left to itself; whereas the joint becomes steadily more stiff if manipulative treatment is used. The recovery of movement is of course slow, and if patients with such injuries are referred to a physical medicine department very few physiotherapists can go on resisting the temptation to push or force the joint. The answer is that no patient with stiff fingers or stiff elbow after injury should be referred to a physical medicine department at all, and that no more should be done than to instruct the patient in his own active ordinary use of the joints.

Exactly the same is true of the shoulder that is stiff after a dislocation of the joint or after peri-arthritis with adhesion formation. Many surgeons are afraid of immobilizing a dislocated shoulder-joint for four weeks, especially in elderly patients, because of their fear of

permanent stiffness; but it is by reason of their fear, and the vigorous manipulative measures they use, that the joints remain stiff. No matter what the age of the patient, a dislocation of the shoulder can be immobilized quite safely with the limb bandaged to the trunk for four weeks provided that thereafter active exercise alone is relied upon. So it is of the shoulder that becomes stiff from peri-arthritis and peri-articular adhesions. I was amazed at the almost universal despair shown at a recent meeting of the British Orthopædic Association as to the prognosis of stiffness of the shoulder from this cause. The fact is that their dismay arose only from the unduly forcible manipulative measures that had been used. If the patient is instructed in the necessary active exercises repeated hourly throughout the day and is seen week by week, or month by month, just to give encouragement, a normal range of movement is regained within about three to six months.

This principle applies also to the knee-joint that is stiff as a result of immobilization in splints or plaster for several months. Many surgeons are unwilling to use the most excellent operation of arthrodesis of the hip, which gives brilliant results, because of their fear of stiffness of the knee; but here again if active exercise is relied upon to the exclusion of forcible manipulation, and the patient is encouraged sufficiently often, an almost normal range of movement is nearly always regained. If the knee-joint is stiff in consequence of a fracture of the shaft of the femur which has necessitated immobilization for some months the danger of forcible manipulation is still greater because the quadriceps muscle has become adherent to the bone at the site of fracture, and if the joint is manipulated there is a considerable danger of fracture of the patella, or avulsion of the ligamentum patellæ, or tearing the insertion of the quadriceps muscle from the patella. Of all the hundreds of stiff fingers, stiff elbows, stiff shoulders and stiff knees that I see after injury or long immobilization I do not manipulate more than two or three a year, and even then only with great caution.

(2) *Manipulation for adhesions after simple strains of the joint.*—Twists of the knee-joint often strain the medial or lateral ligament or the coronary attachment of the menisci, and although the essential treatment is always restoration of muscle control of the joint by static quadriceps exercises there is a small proportion of cases in which pain and local tenderness remain as a result of minor adhesion formation which can be relieved if the joint is gently manipulated under an anæsthetic and the tibia fully rotated on the femur in each direction.

Similarly, after minor sprains of the ankle, adhesions may remain especially on the lateral side between the malleolus and tarsus and recovery is accelerated by a gentle manipulation under anæsthesia. There may be adhesions around the tarsal joints from which recovery can be accelerated by gentle manipulation. When the toe-joints have become somewhat stiff in the clawed position, active exercise is again the basic treatment, but gentle manipulation consisting entirely of traction with flexion of the joints may be beneficial; especially is this true of minor degrees of hallux rigidus. Traction should be applied until a sulcus or dimple of skin is evident at the level of the joint; while the traction is maintained the toe is gently dorsiflexed.

Some years ago Sir Herbert Barker demonstrated to the British Orthopædic Association at St. Thomas's Hospital a series of thirty or forty cases treated by manipulation, and although nearly every knee-joint with torn cartilage, hip-joint with arthritis, shoulder-joint with recurrent dislocation, and very many other of the cases he manipulated under anæsthesia were subsequently operated upon, he did achieve considerable success in patients with hallux rigidus, and also those with tennis elbow in whom the joint was stretched in the direction of cubitus varus with the forearm first supinated and then pronated, the patient's own active exercise being relied upon thereafter.

(3) *Manipulation of osteo-arthritic joints.*—Many surgeons advocate manipulation under anæsthesia of osteo-arthritic joints, but curiously almost all limit such manipulations to osteo-arthritis of the hip-joint. Surely such treatment is entirely wrong. Degenerative arthritis of the hip, which occurs so commonly in middle-aged and elderly patients, is evidence of wear of the joint. The important measure is that the patient should learn to use the joint within the limit of tolerance of activity and not force it beyond that. What good purpose is served by over-driving and over-straining a hip-joint by manipulation rather than encouraging the patient to use the joint with his ordinary activity and recreation within its limit? Forcible manipulation of osteo-arthritic hip-joints never gives more than temporary relief and, indeed, commonly aggravates the degenerative change. The same is true of osteo-arthritis of the intervertebral joints of the spine which need protection from over-use and not force.

(4) *Manipulation of the spine for low back pain and prolapsed intervertebral discs.*—Great success has been claimed by Cyriax and others in the treatment of low back pain by traction-manipulation repeated quite frequently and without any anæsthetic. It is true that if an intervertebral disc is prolapsed a manipulation of this type may replace it with

dramatic success; but it is also true that such manipulation may increase the displacement so that whereas the patient can walk into the department he has virtually to be carried out on a stretcher. In earlier publications such manipulation was said to cure low back pain because it corrected sacro-iliac subluxation; now the same manipulation is acclaimed because it is supposed to correct prolapse of a disc. The fact of the matter is that it is a harmful procedure no matter what the source of the low back pain may be, whether sacro-ileitis, early ankylosing spondylitis, prolapse of a disc or, as in quite a number of cases that I have seen, tumours of the sacrum, tuberculous disease of the sacro-iliac joint or tuberculous disease of the lumbar intervertebral joints. Simple bed-rest and then the protection of a corset achieve far greater success than any type of manipulation.

(5) *Manipulation as an aid to psychological treatment.*—Every patient, no matter how mentally stable and psychologically sound, who has a source of pain develops some degree of psychological reaction by which the pain may be increased especially when miserable, depressed or worried. The common error is to ascribe this to a purely functional disturbance without recognizing the underlying organic disorder. Nevertheless, these functional manifestations are so common, even in the most normal of us, that firm handling, encouragement and reassurance are needed. Sometimes an anæsthetic with gentle manipulation of the affected area assists in the recovery.

There is a centre north of London where apart from insistence on a diet little more than orange juice, a procedure known as "bloodless surgery" goes on. The patient is placed on an operating table and draped with towels; the surgeon scrubs up and dons cap, mask and sterile gloves and then places his hands over the site of pain but never in fact even touches the patient. That is quite probably the best form of manipulative treatment; the more constantly that a physiotherapist can be persuaded to treat a patient without touching, the more certainly will the patient be cured.

Dr. H. A. Burt:

I shall confine my remarks to discussing the value of manipulative treatment in rheumatoid and osteo-arthritis and in the frozen shoulder.

Rheumatoid Arthritis

Two erroneous beliefs about rheumatoid arthritis persist: The first is that rheumatoid arthritis is a disease which "burns itself out" in a matter of a year or two; the second is that it is wrong to manipulate a rheumatoid joint while the disease process in it is active. Some even go so far as to advise against manipulation unless the sedimentation rate is normal.

With regard to the belief that the disease is self-limiting it is admittedly true that there are cases which become inactive within a few months. On the other hand, there are a great many patients in whom activity continues for years and sometimes indefinitely. It is my experience that manipulation may be of the greatest importance for some patients in this long-term group. If manipulation is delayed until the disease is inactive not only is valuable time lost, but the technical difficulties become greater, the procedure is more tedious and painful for the patient, and the results are not so good.

The wrist.—It is very rarely safe or proper to be dogmatic about indications for treatment in any disease but I believe there is one absolute indication for manipulative treatment in rheumatoid arthritis, namely, in the patient whose wrists are becoming fixed in a position of palmar flexion. With the wrist in this position not only is a satisfactory grip impossible, but the likelihood of ulnar deviation of the fingers is very greatly increased. Indeed, I was brought up to believe that a patient who developed a fixed dorsiflexed wrist in the early stages of the disease never developed subsequent ulnar deviation.

A young man developed rheumatoid arthritis in the summer of 1949 and was admitted to University College Hospital in June 1950. At that time both wrists were warm, swollen and flexed and it was not possible to straighten them, let alone put them into a position of dorsiflexion. His sedimentation rate was 25 mm. (Westergren). He was manipulated under anæsthesia in July and again in August 1950, and finally in October 1951. On each occasion the wrists were put into plaster after the manipulation and the patient was ultimately fitted with moulded leather wrist supports. In the X-ray taken in 1955 there is considerable disorganization of both wrist-joints and complete ankylosis of the carpus. He is, nevertheless, able to do light engineering, and his grip is as strong as my own.

It is most unlikely that this satisfactory state of affairs would have come about without manipulation, or if manipulation had been delayed until the disease became inactive.

The knee.—Another indication for manipulative treatment which is almost as important as the last occurs in patients with fixed flexion of the knee which persists or deteriorates in spite of physiotherapy, injections of hydrocortisone or splints.

The technical difficulties of manipulation in such circumstances may be great. With long-standing disease, and particularly in elderly patients, the results are often disappointing. Nevertheless manipulation is usually justifiable, provided that little is done at a time and the manipulation repeated at intervals. Frequently at the first attempt nothing seems to have been achieved but if the procedure is repeated a week later it is often much easier and a significant increase of joint movement is obtained.

The co-operation and willingness of the patient are essential when a number of manipulations are contemplated. This co-operation is only likely to be maintained when anæsthesia is good, plasters, if applied, are comfortable, and post-operative pain properly controlled with analgesics. In fact, with such manipulations, doing only a little at a time, post-operative pain is seldom a serious problem.

I am not convinced from my own experience that injection of hydrocortisone at the time of manipulation is of value; I think it may in fact add to the immediate post-operative pain.

The foot.—It is common for patients with rheumatoid arthritis to complain of pain and discomfort in the feet. If this pain is analysed it will be found in the majority of cases that it does not arise primarily from the arthritis. Rather is it of the same nature as chronic foot strain and arises from the ligaments around the mid-tarsal and less commonly the sub-talar joints of the foot. The importance of mobility in the joints of the foot has frequently been emphasized. It is, as Wiles points out, the key to the problem in certain types of painful feet. "A supple foot", says Wiles (1955) "whatever the habitual posture, seldom causes serious trouble, but a stiff foot, whether it is stiff because of an unresolved sprain, arthritis or contraction of the ligaments, is liable to become painful when subjected to strain." (For a full account of foot strain, Bankart, 1932, should be consulted.)

The only satisfactory method of treating this condition is by manipulation and the results in a large majority of cases are excellent. The results are in fact usually as good as those of manipulative treatment for foot strain due to other causes. It is often unnecessary to use an anæsthetic and satisfactory results follow repeated mild manipulations carried out in the out-patient department. When manipulation of the mid-tarsal and sub-talar joints is performed it is safe to apply a greater force than can be used in the case of other joints. This is in keeping with the belief that here we are dealing with a chronic ligamentous strain rather than an inflammatory condition of the joint.

After manipulation regular physiotherapy is necessary and it is important that passive movements, in particular those NOT under voluntary control, should be given.

Osteo-arthritis

Passing to osteo-arthritis I shall first discuss mobilization of the patella in osteo-arthritis of the knee, and second, the use of traction and distraction in osteo-arthritis of the hip.

The knee.—In osteo-arthritis of the knee, particularly in those cases where there is a superadded traumatic arthritis or peri-arthritis, mobility of the patella is diminished and the peri-articular structures in the infra-patellar region are often extremely tender and sometimes swollen. Gradual progressive manipulation without an anæsthetic, will often mobilize the patella and, in consequence, the range of movement of the knee increases. It is sometimes useful to combine this procedure with injection of the tender peri-articular structures with ½% lignocaine or a mixture of lignocaine and hydrocortisone.

The hip.—In osteo-arthritis of the hip temporary improvement in the mobility of the joint can often be quite painlessly produced without anæsthesia in the following manner. The patient lies supine on the couch and traction is exerted in the long axis of the limb; alternatively momentary traction is applied with the hip held in about 50 degrees of flexion with the knee at a right angle. Such manipulation is a useful adjunct to treatment with sling exercises: it should always be performed whenever lignocaine or hydrocortisone is injected round the joint.

Frozen Shoulder

I shall end with some observations on manipulation in the painful non-arthritic shoulder with limitation of movement—the so-called frozen shoulder. Admittedly this is a controversial subject. It has been stated that manipulation must inflict further damage on periarticular structures, producing increased inflammatory reaction and

pain, and possibly further restriction of movement. It is undeniable that this sequence of events may occur, but it can usually be avoided if movements during manipulation are rigidly restricted to traction combined with rotation.

Forced abduction should never be carried out; this movement aggravates the condition because during its execution there is nipping of the already inflamed bursa, tendons or capsule between the greater tuberosity of the humerus and the under-surface of the acromion.

It is my experience that once the frozen shoulder becomes painless, movements steadily and surely return of their own accord. As a rule, therefore, manipulation of the painless, stiff, shoulder is unnecessary and, incidentally, may bring about return of pain. There are a few occasions when manipulation to improve movement is justifiable, as, for example, in the case of the manual worker where limitation of shoulder movement imposes a definite handicap at work.

The chief indication for manipulative treatment with the frozen shoulder is *persistent* pain. Manipulation should always be considered in cases where pain is increasing in spite of adequate treatment, and especially if nocturnal pain is becoming more severe.

In my experience the injection of hydrocortisone into the shoulder at the same time as the manipulation has not resulted in improvement. There is, however, one situation in which injection of hydrocortisone combined with lignocaine and hyalase is undoubtedly helpful and that is the substance of the pectoralis major, a muscle which is very frequently tender and tight in this condition. I now give this injection as a routine whenever I manipulate a painful shoulder.

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Dr. Guy Beauchamp:

The position of manipulation to-day is very much what it has been for the last fifty years. Those who practise it are satisfied with the results, those who will not or cannot manipulate condemn it. It is a fact that with the well-known manipulators in the past, whether they have been bone setters, osteopaths, or medical men, the world has beaten a path to their door. Sir Herbert Barker, Blake of Charterhouse Square, Bennett of Leamington, Nicholas of Cavelaire, Sir Morton Smart, Marlin and Mennell here in London, are names that spring to mind. The manipulator himself finds this a most satisfying work. Results follow with great speed in the majority of cases and are accepted by the patient with great enthusiasm.

Manipulators fall into three groups:

(1) Orthopædic surgeons; (2) Medical orthopædists; (3) Osteopaths and the subsidiary group of chiropractors.

The techniques of these groups differ widely, by reason of the development of their craft. Orthopædic surgery had its ancestry in bone setters. Medical orthopædists developed manipulation against the background of physiotherapy; osteopaths, the first to practise spinal manipulation, derive from the teaching of Dr. Andrew Still, himself a qualified medical practitioner. His teaching was that in manipulation of the spinal and sacro-iliac joints lay the sovereign method of relieving symptoms. It is not necessary to dwell upon the theories, but it is important to recognize that the teaching in good osteopathic colleges is excellent; anatomy and physiology receive as much attention as in medical school, and the hours of patient learning of techniques might well serve as a reminder of the inadequacy of the young doctor to compete in the field of spinal or other manipulation. It is not an art that can be acquired in six easy lessons, nor will it be learned adequately until some parallel system of teaching is adopted. There is decreasing divergence between certain trends in physical medicine and osteopathic teaching. It would be all to the good if the principle that "structure governs function" were accepted. Indeed what argument can be used against this principle?

So much for the manipulators. Now what of the manipulated? I have recently assessed 300 consecutive patients, who had been referred specifically for manipulation, after examination and diagnosis by their own doctors. Some had had other forms of treatment but most had arrived with an established diagnosis and treatment by manipulation had been asked for by the patient or advised by his doctor. We can see therefore the type of case for which manipulative treatment is likely to be sought.

The first interesting point was that with a great number manipulation was chosen as the initial treatment, whereas ten years ago they would have already run the gamut of physio-

therapy. This is a great advance, and it is certain that the teaching and writings of Mennell and Cyriax have been largely responsible for this.

There was a predominance of females over male, 58% female, 42% male, and less than half (151) complained of low back pain, and of these only 43 could be positively diagnosed as intervertebral disc propulsions. These figures do not support the contention that most backache is due to a disc lesion. In this number of disc lesions there was no disproportion between male and female, but in the other groups where backache was due to other causes there were twice as many females as males. Sacro-iliac strain accounted for 59, the females predominating by 10·6% over 6·3% males.

The next largest groups were those complaining of pain in the neck and shoulder girdle. Cervical spondylosis accounted for 66 of these, 10% male and 8% female.

The next largest group in this division was of derangement of the occipito-atlantal and atlanto-axial joints, occurring without spondylosis or other recognizable pathology. These accounted for 18% of the total; 5·4% male and 12·9% female. This group is one of the most fascinating and rewarding in the manipulative field and although it has received scant attention in the past, manipulation is the only satisfactory treatment. The signs and symptoms are characteristic. Limitation of mobility in varying degree, pain referred to occipital, frontal or parietal area, hemicrania, hypertension, tinnitus, giddiness, alteration in the special senses and profound fatigue being the usual manifestations, and occurring in variable degree and combinations. Treatment by manipulation is easy for the patient in the majority of cases; though the technique is tricky a single treatment may suffice and effect an immediate cure. So-called idiopathic hypertension is closely linked with this group and of the 350, 5 patients with hypertension presented themselves for treatment. Some of these had recognizable mechanical disabilities, the correction of which was effective in relieving their hypertension. Where no derangement was found, hypertension was unaltered by treatment.

It is certain that where a subluxation occurs imbalance of muscle action must occur and there then follows a reduction in the blood supply to the malfunctioning tissues. There will also be increasing loss of function and of elasticity. Avascularity may extend far beyond the affected area and be responsible for most of the subjective symptoms of these conditions.

It is my belief that all patients who have manipulative treatment need exercises afterwards. It was the late Sir Morton Smart who said that manipulation without exercises was useless. This I think is a little exaggerated, but it serves to drive home the necessity of such after-treatment. Massage and heat play no part at all in recovery after manipulation; it is for the most part a waste of time and money and often greatly delays recovery.

In none of these 350 patients was any anæsthetic used, nor would it have been particularly safe to manipulate under anæsthesia the occipito-atlantal and atlanto-axial subluxations. The manipulative thrust is made with the patient in the sitting position, the head of the patient is extended and the thrust is an upward and backward screw movement. Considerable force is used through a minute distance and is certainly not to be used without some voluntary positional control. Occasionally and especially in children, where fear or pain are dominant, it may be necessary to use an anæsthetic for upper cervical joint lesions, but the majority of treatments can be made without anæsthesia.

Dr. A. T. Richardson:

Although pain referred from spinal structures is one of the commonest symptoms complained of by patients attending orthopædic and physical medicine departments, it is in only a few that a causative lesion can be demonstrated with any certainty. For the remainder an extraordinary number of diagnoses and treatments have been suggested. Formerly when fibrositis and other terms, implying at the most a non-specific inflammation of various soft tissues, were popular, no more than the application of harmless analgesics and heat seem indicated. In contrast the diagnosis of prolapsed intervertebral disc, which is now frequently applied to any spinal pain of undetermined origin, so frequently in fact that it is rapidly becoming devoid of any pathological implications, suggests a specific mechanical derangement. This has led not only patients but also medical practitioners to enquire about the possibilities of manipulative replacement of "slipped discs". Many of the doctors, to judge from some of the 36 letters which followed an article by Cyriax (1955) are remarkably enthusiastic about this form of treatment.

In theory, manipulation can be effective in relieving pain caused by replaceable displacements and by fibrous adhesions in and around a joint or attached to a normally mobile structure. Unless one of these conditions exists and can be diagnosed and unless it can be ensured that manipulation will have the desired effect without producing any harmful results, it is not indicated.

These criteria would seem to be satisfied in only a limited number of the patients afflicted with pain of spinal origin who attend hospital as out-patients. Thus, while the diagnosis of vertebral disease can be firmly made on the basis of the typical clinical and radiological appearances, there are no displacements or adhesions to manipulate, except, perhaps, following fractures. As regards painful disease of the intervertebral joints, while ankylosing spondylitis has typical clinical and radiological signs, degenerative joint disease of the spine generally has no characteristic clinical signs and is such a common radiological finding in the older age group that it is difficult to relate it to pain in any particular case. Exceptions to this are, first, in the uncommon event of degenerative disease of the cervical neurocentral and apophysial joints occurring as part of a primary generalized osteo-arthritis. In this event, as is the case with osteo-arthritis of the peripheral joints, manipulation is not often called for except when mobilizing exercises have failed to restore mobility. The second occasion when pain can be related to degenerative changes is when it is associated with symptoms of pressure on nerve roots or spinal cord. Here manipulation is fraught with risk by virtue of the fact there is no way of protecting the already damaged spinal cord or nerve roots from increased damage by manipulation.

The remainder of cases of spinal pain are made up of a group which has little variety in symptoms, no specific signs, equivocal X-rays and negligible pathology and which, therefore, as I have said, attracts many diagnostic labels. However, within this group the clinical entity of acute lumbago, acute cervical pain and perhaps acute dorsal spinal pain are recognized. The essential features are pain of acute onset, often recurrent, which is produced by movement of the relevant part of the spine which is held rigidly. There are no symptoms or signs of cord or nerve root pressure and X-rays show no more than loss of the spinal curve or perhaps the usual degenerative changes if the patient is in the older age group.

While the exact nature of the lesion or lesions causing these syndromes is a matter of controversy, there is an increasing body of opinion which associates them with mechanical abnormalities of the intervertebral joints. Particularly in favour of this concept is the occasional occurrence of pain of fulminating onset and equally sudden remission, which suggests a mechanical derangement and not an inflammatory state. As to the type of articular derangement, some stress the importance of the apophysial joints, and infer nipped synovial fringes, loose bodies or subluxation in these joints (Crisp, 1952), but to most the intervertebral disc is the root of all evil. The theory that intervertebral disc lesions are the common cause of acute spinal pain of this type is largely based on the fact that in some cases pain eventually radiates in root distribution, is accompanied by signs of nerve involvement and so presents the accepted clinical picture of intervertebral disc degeneration. If, in fact, the lesion of acute spinal pain of this type is a mechanical derangement of the apophysial joints, manipulation would seem the only form of direct attack on the lesion and should be harmless. If, in fact, the underlying lesion is disc degeneration the place of manipulation is more debatable. However, whether it be considered that the pain is due to disc prolapse with bulging of the posterior ligament and perhaps dural pressure (Cyriax, 1945) or displacement and impaction of a nuclear sequestrum (Armstrong, 1952), if it is believed that these can be replaced by manipulation without the risk of damage to nerve tissues, the treatment would seem justified.

The ætiology of chronic spinal pain in which no definite and significant lesion can be demonstrated is even more speculative. Some cases derive from trauma, others from recurrent acute attacks, and in yet others postural abnormalities or degenerative articular changes seem to be responsible. Psychological factors are constantly present and sometimes dominate the clinical picture. It follows that the theoretical indications for manipulation are even more difficult to define, but it would seem reasonable that where loss of spinal movements has occurred and has not been restored by mobilizing exercises manipulation may be indicated, the object being to stretch or break any fibrous adhesions or capsular contractions contributing to the immobility and pain, and not for psychological reasons!

Whatever the theoretical considerations for manipulation, widespread acceptance of this form of treatment must depend upon results. It has been argued that manipulation of the spine is so often carried out by lay practitioners that some patients must benefit in some way and indeed we have all seen patients, even doctors, who appear to be reliable witnesses and who state their symptoms have been relieved by manipulation. However, it is equally common to meet patients who trace the onset of their symptoms to manipulation or who state they have had more pain, often of root distribution and accompanied by paræsthesiæ, etc., following this form of treatment. Reference to the literature shows that opinions on spinal manipulation range from that of Cyriax (1955) who states that unilateral scapular aching associated with pain on moving the neck can be relieved in 99% of cases by one or two sessions of manipulation and that "in backache manipulative treatment, without anæsthetic, is usually successful" to Charnley (1955) who in discussing acute lumbago and sciatica does not recommend manipulation at all, although he states "the sequestrum type of lumbago is the one which has sometimes been relieved by manipulation". The more

general view is perhaps that expressed by Coltart and Osmond-Clarke (1955) who state "we have found that quite a few cases of acute low back pain with fixation (lumbago) can be relieved immediately by single manipulation without anæsthesia if seen early enough" and similarly Wiles (1955) discussing acute lumbago states "manipulation is a simple method of treatment and relieves many acute attacks almost at once" and discussing acute stiff neck says "an attack can usually be terminated quickly by manipulation".

Unfortunately only one controlled investigation into the place of manipulation in spinal pain, in fact in backache, has been published, by Coyer and Curwen (1955). They treated alternate cases either by manipulation or by bed-rest with a lumbar pillow and analgesics, rejecting only those showing root pain, signs of nerve root pressure, or X-ray changes other than congenital abnormalities or degenerative changes. The design of the experiment has been criticized and doubt over the final result in 16 patients of the control group of 76 has reduced the statistical significance of their figures, nevertheless, three conclusions would seem to be justified from their results. First, that with the bed-rest regime this type of backache remits within a few weeks. Thus, they were able to discharge 50% of their control cases pain free at the end of one week, 60% at the end of three weeks and at six weeks only 28% had symptoms. Second, they recorded no adverse effects following manipulation of 76 patients although this manipulation was carried out in some instances by physiotherapy students. Third, that while the results of manipulation were better than those produced by bed-rest alone, their results do not support the claim of the uncritical enthusiasts that manipulation is the panacea for all backache. Finally I must emphasize the necessity for X-rays before manipulation particularly in view of the amount of this treatment being carried out by general practitioners who have no access to X-ray facilities. Occasionally serious lesions of the spine present as acute neck pain or lumbago without neurological involvement; the manipulation of them can be disastrous.

I conclude, therefore, that on theoretical grounds and from published results for what they are worth, the conditions for the effective and harmless use of spinal manipulation are likely to exist in the early stages of acute spinal pain in which no neurological signs and symptoms are present and X-ray shows no significant disease. There may also be a case for manipulation of the chronically painful spine with immobility in which no specific lesion can be found and where mobilizing exercises have failed. However, the need for an adequate investigation into this form of treatment is obvious and until this has been done I feel the creation of enthusiasm for this form of treatment in the ranks of physiotherapists is to be deprecated. I have no doubt that analgesics, bed-rest, corset or neck collar and various forms of physiotherapy remain the mainstay of treatment of spinal pain.

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Section of Pathology

President—Professor JOHN W. S. BLACKLOCK, M.D.

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The Incidence of Primary Hepatic Carcinoma in Cirrhosis

By R. G. F. PARKER, M.D.

Bernhard Baron Institute of Pathology, London Hospital

IT will be argued in this communication that in England malignant change complicates cirrhosis oftener than is generally appreciated. The last detailed report on the subject from this country was that of Stewart (1931), who found primary hepatic carcinoma in 3·41% of all cirrhotics (or in 7·3% if slighter cases were excluded). Since then there have been only passing references to suggest that the incidence in England, and in Europe generally, may in fact be considerably greater than this.

It is important to the thesis which is to be developed here that criteria for the pathological diagnosis of cirrhosis should be clearly defined. There has been a strong tendency in recent years (*see*, for instance, the Report on the Fifth Pan-American Congress of Gastroenterology, 1956, *Lancet*, i, 377) to accept only those lesions in which the normal lobular pattern of the liver has been replaced by nodules of regenerated parenchyma separated by a more or less well-developed reticulum of fibrous tissue. Disorganization of normal lobular architecture is the essential feature of cirrhosis, fibrosis being fundamental only to the extent that it contributes to this. It follows that minor grades of hepatic fibrosis with a normal lobular pattern should not be called cirrhosis. This definition of cirrhosis has a sound theoretical basis (Parker, 1956); it also has the great practical merit that it brings into close accord the clinician's and the pathologist's concepts of the condition. One is bound occasionally to encounter borderline lesions in which the normal lobular pattern has not been entirely destroyed: these, however, are nearly always incidental—and often unexpected—findings at necropsy, although in some cases of post-necrotic cirrhosis (the healed yellow atrophy of older writers)—there may be some retention of lobular pattern in the regenerated parenchyma even though in other respects these cases may be both clinically and pathologically fully developed examples of cirrhosis.

In all but one of the hepatic carcinomas accompanying cirrhosis in this series the diagnosis of malignancy was established by the presence of extrahepatic metastases or of invasion of veins within the liver (frequently both these features were found). In the single exception it rested upon cytological atypicality alone.

In Table I are analysed all cases of primary hepatic carcinoma coming to necropsy in the

TABLE I.—CLASSIFICATION OF PRIMARY HEPATIC CARCINOMA, (LONDON HOSPITAL, 1919–1955)

Morphological category	Total	Number associated with cirrhosis	Number occurring in males
Liver-cell carcinoma	32	27 (84·4%)	29 (90·6%)
Bile-duct carcinoma:			
hilar in 11; peripheral or multinodular in 6..	17	1 (5·9%)	11 (64·7%)
Histologically doubtful carcinoma	3	1 —	1 —
Mixed liver-cell and bile-duct carcinoma ..	1	1 —	1 —
Total	53	30 (56·6%)	42 (79·2%)

London Hospital from 1919 to 1955. There were 53 such cases among 17,732 necropsies, an incidence of 0·30%, which is not unusual (Berman, 1951; Meyer, 1954). In other respects, too, the figures in Table I could be matched in whole or in part by those of many previous reports. Thus the high incidence of cirrhosis as an accompaniment of liver-cell carcinoma is well known, as is the fact that most patients with this type of carcinoma are men. Of 30 carcinomas associated with cirrhosis in this series, 27 were in males. Although this striking differential sex incidence is well recognized, its implications have not always been appreciated.

In Table II the problem has been approached from the opposite viewpoint, namely the

TABLE II.—INCIDENCE OF CARCINOMA IN CIRRHOSIS

	Total	Number with carcinoma
All cases of cirrhosis diagnosed at necropsy	184	30 (16·3%)
Fatal cirrhosis	134	25 (18·6%)
Incidental cirrhosis	50	5 (10·0%)

incidence of primary hepatic carcinoma in a series of cirrhotics. In the years 1919 to 1955, 184 cases of cirrhosis came to necropsy at the London Hospital, and in 30 (16·3%) of these there was malignant change. This is a figure some four times greater than the lower of those given by Stewart (1931), or than that usually accepted in the American literature (Gall, 1956). When one considers only those cases in which cirrhosis was more or less directly the cause of death (termed fatal cirrhosis in Table II) the incidence of carcinoma is even higher, namely 18·6%.

The sex incidence of carcinoma complicating cirrhosis is considered in Table III. It will

TABLE III.—CARCINOMA AND CIRRHOSIS—SEX INCIDENCE

	Total	Number with carcinoma
All cases—males	114	27 (23·7%)
All cases—females	70	3 (4·3%)
Fatal cirrhosis—males	74	22 (29·7%)
Fatal cirrhosis—females	60	3 (5·0%)
Incidental cirrhosis—males	40	5 (12·5%)
Incidental cirrhosis—females	10	0 —

be seen that malignant change occurs among male cirrhotics far more frequently than among females, the respective percentages for fatal cirrhosis being 29·7 and 5. In the series as a whole, 23·7% of males developed hepatic carcinoma.

In Table IV cases of fatal cirrhosis are divided on an ætiological basis. Incidental cirrhosis

TABLE IV.—CIRRHOSIS AND CARCINOMA—ÆTIOLOGICAL CLASSIFICATION

Ætiological category	Fatal cirrhosis Total number	Number with carcinoma
Cause undetermined	61	10 (16·4%)
Post-hepatitic cirrhosis	36	1 (2·8%)
Post-necrotic cirrhosis in 25 (a history of hepatitis in 15 of these); Laënnec's cirrhosis in 11		
Alcoholism	30	10 (33·3%)
Hæmochromatosis	2	2 —
Primary biliary cirrhosis	2	0 —
Fanconi's disease	1	1 —
Chiari's syndrome	1	1 —
Cinchophen poisoning	1	0 —
Total	134	25 (18·6%)

has been excluded from this analysis because of relative inadequacy of the clinical records. It will be seen that even in fatal cirrhosis there was a substantial number of cases, nearly one-half, in which there was no reliable clue to the ætiology of the hepatic lesion. Post-hepatitic cirrhosis accounted for about a quarter of the total, and in this group the incidence of carcinoma was very low. Although the criteria adopted for including lesions in this category were fairly strict, it is apparent that the diagnosis was not equally well established in all cases. The only example of primary hepatic carcinoma in this group occurred in a man of 60 with Laënnec's cirrhosis and a history of jaundice forty years previously. It cannot of course be proved that the jaundice and cirrhosis were causally related. There are in the literature examples of post-hepatitic cirrhosis complicated by carcinoma (Walshe and Wolff, 1952; Sheldon and James, 1948), but the figures cited here, taken with those of Stewart (1931) suggest that malignancy rarely supervenes upon this type of cirrhosis. The rather higher proportion of females in the post-hepatitic cases than in the series as a whole may have a bearing on this. More important perhaps is the relatively short duration of post-hepatitic cirrhosis (or at least of those cases in which the diagnosis can readily be made). In the 15 examples of post-necrotic cirrhosis with available clinical data included in Table IV, the average interval between the initial attack of hepatitis and death from cirrhosis was only three years.

In chronic alcoholism, on the other hand, the incidence of carcinoma in this series was very high, namely 33·3%. In comparing alcoholic and non-alcoholic cirrhosis a figure of this magnitude was liable to occur by chance in only 1 of every 25 samplings. But after allowing for the fact that 24 of the 30 alcoholics, including all those with carcinoma, were males, the possibility of this difference having occurred by chance was raised to about 1 in every 7 samplings. It is quite possible therefore that the high incidence of malignant change among the alcoholics of this series merely reflected the sex incidence of alcoholic cirrhosis. The supposed high incidence of liver cancer in hæmochromatosis may have a similar explanation, for hæmochromatosis is very largely a disease of males. Warren and Drake (1951) deduced from the literature that this incidence was 18·9%, a figure which they considered to be more than four times that for cirrhosis in general; this figure is, however, appreciably less than that for males in the present series.

Finally an explanation must be sought for the differences between the figures set forth here and those in previous reports on the subject. It may well be that many of these differences are apparent rather than real, being due to use of the term cirrhosis for minor degrees of hepatic fibrosis without disruption of lobular pattern and without the clinical picture of the disease. It is claimed, however, that there are geographical variations in the liability of cirrhosis to undergo malignant change (Report of Conference on Liver Cancer, 1956, *Lancet*, ii, 782). In North America this liability is said to be lower than in Europe; but there is in the literature some evidence to the contrary. Thus Edmondson and Steiner (1954) found hepatic carcinoma in 4·5% of all cirrhotics, but in 19% of advanced atrophic cirrhosis. The corresponding figures of Wilbur *et al.* (1944) are 10·5 and 14·2%. Figures in excess of 10% are also given by Loesch (1939) and McNamara *et al.* (1950). Thus it may well be that uniform standards for the diagnosis of cirrhosis would result in similar figures for both America and Europe. Carcinoma as a complication of cirrhosis in tropical countries will not be discussed here.

Summary

Primary carcinoma of the liver was present in 16·3% of 184 patients in whom cirrhosis had been diagnosed at necropsy. When only those patients actually dying of hepatic disease were considered, the incidence of malignant change was 18·6%. Corresponding figures for male cirrhotics alone were 23·7 and 29·7% respectively.

Post-hepatitic cirrhosis is seldom complicated by primary hepatic carcinoma. Its high incidence in alcoholic cirrhosis and in hæmochromatosis may depend on the fact that most patients with these diseases are males.

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Pseudocholinesterase in Early Infancy

By H. LEHMANN, M.D., Ph.D., F.R.I.C., JOSEPHINE COOK, M.B., B.S., D.C.H., and ELIZABETH RYAN, B.Sc.

St. Bartholomew's Hospital, London

PSEUDOCHOLINESTERASE

PSEUDOCHOLINESTERASE is an enzyme present in the serum which destroys acetylcholine *in vitro*. It is not identical with the true cholinesterase of the red cells which hydrolyses acetylcholine at physiological concentrations. We determined the activity following Jones and Tod (1935) and McArdle (1940) by incubating serum with acetylcholine and a $NaHCO_3$ buffer in a micromanometer. On hydrolysis of acetylcholine to choline and free acetic acid one mol of CO_2 is liberated from $NaHCO_3$ for each mol of free acetic acid, and the CO_2 is measured manometrically. According to McArdle (1940) one unit of enzyme equals one μl. of CO_2 liberated by one ml. of serum in one minute at 37° C. Our normal range in adults is 75–125 units with a mean of 85 units.

Normal Pseudocholinesterase Levels in Adults, Children and Infants

It is well known that the normal pseudocholinesterase level shows great individual variation in adults, although it remains very stable from day to day in any one individual (Vereby, 1936; Hall and Lucas, 1937; Antopol *et al.*, 1937; McArdle, 1940; Sawitsky *et al.*, 1948; Callaway *et al.*, 1951; Kaufman, 1954). There is in adults no correlation between age and pseudocholinesterase level. The normal level in children is not as well defined as that of adults. Rather high values have been reported in children by McArdle (1940) who in 40 normal adults found a range between 51 and 121 units with a mean of 78, and in 20 children aged between 7 and 15 years observed a range between 71 and 166 units with a mean of 105 units. Although there is a considerable overlap between the values found in the two groups the overall difference is statistically significant. Hodges (1956) compared 52 healthy adults and 70 healthy children aged 3–10 years. The number of high values was greater among the children, but the differences were not significant statistically. Our own experiences are the same as those of Hodges. In contrast to children where the pseudocholinesterase level is if anything higher than in adults, low enzyme activity has been reported in newborn infants by Faber (1943) and McCance *et al.* (1949). Stead (1955) mentions that he has found the pseudocholinesterase level of the neonate at times to be as low as 40% of the adult mean.

Liver Function and Pseudocholinesterase Level in the Newborn

It is now accepted that a low pseudocholinesterase level can be an indication of lowered liver function. McArdle (1940), Wescoe *et al.* (1947), Kaufman (1954) and Hunt and Lehmann (1956), among others, have demonstrated the changes of pseudocholinesterase level with improvement or deterioration of liver function. It occurred to us that the low pseudocholinesterase level found at birth might be related to incomplete development of liver-cell activity—just as functional immaturity of the liver cell has been held responsible for the physiological hæmolytic jaundice of the newborn, the liver at birth being thought to be unable to metabolize an amount of bilirubin arising from red cell breakdown with which it would easily cope at a later age.

Mollison and Cutbush (1949) injected 5 mg. of bromsulphalein per kilogram of body weight into healthy adults and found that the liver removed 98% of the drug from the blood stream within one hour. In newborn infants receiving the same dose there was an average retention of 15% of the dye two hours after the injection. These results were interpreted as an indication of an immaturity of the excretory function of the newborn liver. They were in support of earlier work of Herlitz (1926) who also had described an abnormal bromsulphalein retention in the newborn, but they contradicted the observations of Salmon and Richman (1943) who had failed to do so. Yudkin *et al.* (1949) tested the bromsulphalein excretion in infants from 8 hours to 8 days old and found a higher proportion of normal values above the age of 4 days than below that age.

To obtain exact information on the pseudocholinesterase levels of infants seemed to us valuable not only for theoretical reasons but also from the practical point of view. In the diagnosis of neonatal hepatitis it is important to know what constitutes an abnormally low level in infants. Mollison and Cutbush (1949) and Yudkin *et al.* (1949) had not found a correlation between the degree of failure to excrete bromsulphalein at birth and the subsequent rise in bilirubin levels. We had hoped that the pseudocholinesterase level at birth might perhaps serve as a measure predicting the failure to metabolize bilirubin later on.

Results

We examined 87 cord bloods of which 43 were obtained at St. Bartholomew's Hospital and the remainder from Queen Charlotte's Maternity Hospital. It will be seen from Table I

Table I.—Pseudocholinesterase and Birth Weight

Weight lb.	Number	Mean (units)	Range (units)	Number	Mean (units)	σ
2–3	9	55	35–104			
3–4	10	55	37– 81	43	59	±15
4–5	24	62	34– 93			
5–6	16	62	36– 86			
6–7	13	55	38– 71	29	59	±13·3
7–8	9	66	38–110			
8–9	6	76	41–101	15	70	±22·2

Pseudocholinesterase levels in newborn infants.

that many values were below those considered normal in adults. The mean value was higher the greater the birth weight, but with all birth weights the lower range extended below the

normal adult range. In 61 of the 87 children definite information could be obtained on the duration of gestation, in addition to that of the birth weight. Table II shows that there was

TABLE II.—PSEUDOCHOLINESTERASE IN INFANTS

Age	Number	Mean (units)	Range (units)	σ
At Birth				
Premature ..	30	59	35–104	±16·6
Full term	31	66	38–110	±17·2
1–4 weeks	10	86	60–105	±15·9
4–8 weeks	14	94	68–150	±21·9

no difference when cord bloods of 30 premature and 31 full term babies were compared. Of the premature babies 6 had been born after a pregnancy lasting less than 30 weeks, and 24 after one lasting 30–35 weeks. There was also no difference in the results obtained in these two groups of premature infants. Table II also shows that in contrast to the newborn the pseudocholinesterase level in infants aged 1–8 weeks was within the range considered normal for adults and that in the group aged 4–8 weeks there was a number of children with a level higher than normal adult levels.

In view of the wide individual variation a much larger number of infants would have to be investigated to obtain statistically significant data supporting a rise of pseudocholinesterase level within the first few weeks of life. We decided therefore to examine the enzyme levels over the first weeks of life in 22 infants individually. These had been born at full term with a normal birth weight and were not jaundiced. Fig. 1 illustrates the results; the values

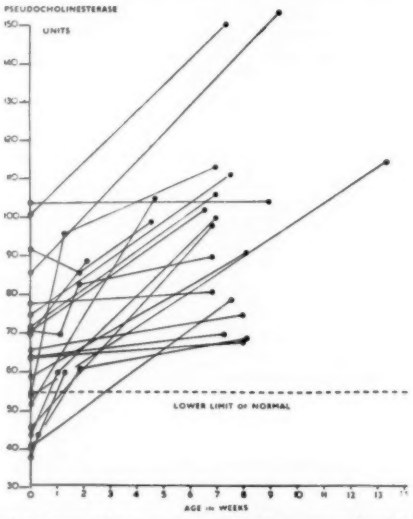


FIG. 1.—Serial observations on pseudocholinesterase level in 22 normal infants during the first weeks of life.

obtained at birth (but not those obtained later) are also included in Tables I and II. It will be seen in Fig. 1 that 8 of the 22 infants showed levels of 55 units and below at birth, and that the highest level was 104 units. With one exception, where at birth and just above nine weeks later the level was 104 units, all infants examined after one month showed a higher enzyme concentration than at birth. Within the second month of life all of 20 infants seen were found to have levels within the normal range. Furthermore whereas at birth only three values of 22 had been above 90 units, within the second month of life 13 of 20 were above this level.

The samples obtained at birth were cord blood, and those obtained later were capillary blood. Fig. 1 illustrates that the change from the enzyme concentration at birth to that seen later was gradual and could not be due to a difference between cord and capillary blood. It will be seen that in one instance the level rose from 38 units at birth to 44 units after two and to 60 units after nine days.

Unfortunately no correlation between pseudocholinesterase level at birth and subsequent rise of bilirubin level was found. On the other hand our observations allow the suggestion that except for the first few days of life a low pseudocholinesterase level can be taken to be pathological in infants as well as in adults. This conclusion has helped us on several occasions in the diagnosis of jaundice in infants, and has so far never failed us.

Conclusions

The pseudocholinesterase level was measured in the serum of 87 newborn infants. Whereas in adults the normal range is 55–125 units, the range in the newborn was 34–110 units. There was no difference between premature and mature newborn infants, and no correlation could be found between pseudocholinesterase level at birth and subsequent rise in bilirubin level.

In 24 normal infants aged 1–8 weeks the range was 60–150 units, and the low pseudocholinesterase level at birth is correlated with an immaturity of liver function as previously demonstrated by the measurement of bromsulphalein excretion.

Serial observations were made on 22 infants. 8 of them at birth had pseudocholinesterase levels lower than would be considered normal in adults. All values were normal when the infants were re-examined later on. Whereas only 3 of the infants had at birth a pseudocholinesterase level above 90 units, 13 such values were found in 20 infants re-examined within the second month.

It is suggested that after the first few days of life an abnormally low level of pseudocholinesterase can be considered pathological.

Acknowledgments

We should like to thank Dr. C. F. Harris and Dr. A. White Franklin for permission to investigate infants under their care and Dr. G. H. Lathe for sending us sera from infants under examination for jaundice in the Bernhard Baron Laboratories at Queen Charlotte's Maternity Hospital.

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Section of Surgery

President—ERIC A. CROOK, M.A., M.Ch., F.R.C.S.

[*November* 7, 1956]

Post-Traumatic "Tumour" of Stomach.—J. T. CHESTERMAN, F.R.C.S.

This patient, a well-built man aged 29 and a fitter erector by occupation, fell prone some 12 ft. off scaffolding and while lying on the ground, a 15-cwt. metal container rolled across the left lower chest, pinning him down.

I first saw him some eight hours later when his presenting symptom was dyspnœa. He had a tension pneumothorax on the left side but no fracture or other obvious gross lesion. The tension pneumothorax could not be relieved for more than one hour or so by needle aspiration so an intercostal catheter was inserted. However, some hours later he suddenly became breathless again so a little barium was given by mouth and a further X-ray film taken which showed the stomach and intestine herniated into the left thoracic cavity. Also, he developed hæmaturia and right-sided renal pain.

At thoracotomy (6.2.54), the stomach, parts of the small and large intestine were reduced, the spleen was removed on account of a tear in the upper pole, which, however, had not bled, and the diaphragm was sutured. No gross lung lesion was found. Recovery was uneventful and the patient returned to work fourteen weeks later.

Seven months after the accident he started suffering from acid regurgitation only when lying down and after taking certain foods such as pastry and plums, but by a year later posture alone was the determining factor in the occurrence of regurgitation. This did not bother him much until two and a half years after the accident, when vomiting started to take place at any time and in any position and was associated with epigastric cramp, perspiration, throbbing in the head and trembling in the legs. Relief only occurred after vomiting about 5 oz. of what appeared to be gastric juice. (Routine blood and urine analyses showed nothing abnormal.)

A Ba meal examination suggested a lesion in the fundus of the stomach (*see* Fig. 1). Gastroscopy showed hypertrophic folds running towards the fundus but was not conclusive. A diagnosis of benign tumour was made.



FIG. 1.—Barium meal showing localized muscular hypertrophy of the fundus of the stomach at the site of adhesion to the diaphragm.

Operation (16.10.56).—The stomach was approached through the old thoracotomy incision and a localized mass felt through its wall exactly opposite to an area of dense non-vascular fibrous union of the fundus of the stomach to the diaphragm. The stomach was freed and the "tumour" excised. Recovery has been uneventful and the patient can now take normal diet and remain in any position without discomfort (7.11.56).

Pathological report.—"A piece of gastric mucosa. Does not look markedly neoplastic but the muscle tissue seems abundant. Histological examination shows an intact but rather hypertrophied mucosa. Beneath this is a mass of normal-looking smooth muscle. It is not encapsulated and merges into the surrounding tissue. Groups of sympathetic ganglia are identifiable in the interstices. This suggests to me that this is not a true leiomyoma but a localized hypertrophy."

CONCLUSION

This appears to be a localized muscular hypertrophy of the stomach at the site of a fibrous union with the diaphragm which gave rise first to incompetence of the cardia and later, intermittent obstruction.

Neurofibroma of the Sacral Plexus.—R. S. HANDLEY, O.B.E., F.R.C.S.

A woman of 25 complained that since the age of 10 she had suffered intermittent "electric" pains shooting down her left leg sometimes reaching the great toe. They were worse if she were constipated or if she lay on her left side. The pains had recently increased to the point of being a considerable nuisance. No orthopædic cause for the symptom was found by Mr. Philip Kerr, F.R.C.S., who referred her, but he had discovered a mass in the pelvis.

Full examination showed no abnormality except for the pelvic mass, which was clearly extra-rectal, fixed to the side wall of the pelvis, smooth, rubbery-hard, and apparently about the size of a flattened hen's egg. Palpation of it *per rectum* caused the tingling pain down the leg of which the patient complained. A sacral plexus neoplasm, probably a neurofibroma, was diagnosed.

With the patient in a steep Trendelenburg position, the peritoneal cavity was opened by a low left paramedian incision. The upper half of the tumour was easily seen. The peritoneum over it was incised and it was enucleated by blunt dissection, mostly with the finger. Venous oozing was checked by a pack, followed by implantation of gelfoam. Apart from a small hæmatoma, recovery was uneventful and the symptoms were completely relieved.

The specimen was a faintly lobulated tumour, measuring 3 in. by 2 in. by 1 in. and sections showed a typical, fairly cellular neurofibroma.

Traumatic False Aneurysm of the Posterior Tibial Artery.—E. C. B. BUTLER, F.R.C.S.

Male, aged 21. Four months before admission, patient had sustained a fractured right tibia and fibula which had been treated by plating. For six weeks there had been increasing swelling and aching of the right calf.

On examination.—There was good union of the fractured bones, and an obvious swelling of the right calf which had a bruit on auscultation. Arteriogram confirmed the presence of a large aneurysm arising from the posterior tibial artery.

11.1.56: A vertical incision was made down the back of the calf splitting the gastrocnemius and soleus muscles. A large false aneurysmal sac was found over which was stretched the posterior tibial nerve. When the clot had been cleared away a small hole was seen in the posterior tibial artery; this was still patent and pulsating. The posterior tibial artery was ligated. Directly under the site of the injury to the artery was the point of a screw. The wound was sutured with drainage. The patient made a good recovery and had excellent arterial circulation to his leg.

Comment.—(1) The injury to the artery may have occurred at the time of operation or it may have been due to gradual erosion of the posterior tibial artery by the point of the screw. (2) The approach to the aneurysm by splitting the soleus and gastrocnemius muscles gave an excellent exposure without damaging the ultimate functions of these muscles.

Malignant Hæmangioblastoma of Liver. Total Excision of Right Lobe of Liver.—RODNEY SMITH, M.S., F.R.C.S.

Mrs. E. P., aged 65. Five months' history of breathlessness, exhaustion, swelling of abdomen, swelling of ankles, pain in upper right abdomen. Examination revealed huge irregular enlargement of liver. Liver function tests normal. X-ray of chest showed gross elevation of right diaphragm. Liver biopsy attempted twice. Blood-stained fluid obtained. Cholecystogram: No gall-bladder seen.

Operation I (14.10.56).—Upper right paramedian incision. Huge cystic tumour occupying whole of right hepatic lobe. Left lobe apparently clear. Evisceration, packing and marsupialization of largest cyst, with piece of wall for biopsy. Report: Malignant hæmangioblastoma.

Operation II (1.11.56).—Hypothermia induced. Right thoraco-abdominal incision. Total excision of right lobe of liver (Fig. 1).

Procedure.—Dissection in the porta hepatis, ligation of cystic duct, right hepatic duct, right branch of hepatic artery, right branch of portal vein. Division of peritoneal attachments of right lobe. Liver divided between right and left lobes with great care in order to secure all right hepatic veins draining into the inferior vena cava and preserve the middle and left hepatic veins. Detached right lobe removed. Abdomen closed with drainage.



FIG. 1.—Resected right lobe of liver. Dotted area shows line of section between right and left lobes.

Progress.—Liver function tests on the fourth post-operative day gave normal values. Patient has made a good recovery, but a rare complication of hypothermia (venous gangrene of a hand) has led to a longer stay in hospital than expected.

(A detailed report of this case is to be published elsewhere.)

The following Cases and Specimens were also shown:

Ossification in a Lipoma of the Thigh.—Mr. G. S. PLAUT. **Unusual Duplication of the Ileum.**—Mr. P. T. SAVAGE. **Mucus-secreting Carcinoma of the Ileum.**—Mr. J. G. JAMIESON. **Ligature of the Inferior Vena Cava during Nephrectomy followed by Complete Recovery.**—Mr. L. R. LEASK. **Hour-glass Stomach with Pyloric Carcinoma.**—Mr. A. R. ANSCOMBE. **Massive Recurrent Infected Ventral Hernia.**—Mr. K. OWEN. **"Retention Cyst" of the Colon.**—Mr. RICHARD E. SHAW. **Gas-filled Pseudo-diverticulum of Sigmoid Colon.**—Mr. G. WESTBURY. **Crohn's Disease in Ascending Colon.**—Mr. J. E. S. SCOTT. **Unusual Carcinoma of the Pancreas in a Man of 26.**—Mr. RODNEY SMITH.

[*December* 5, 1956]

DISCUSSION ON THE PROBLEM OF THE RESISTANT ORGANISM AND CHEMOTHERAPEUTIC SENSITIVITY IN SURGERY

Professor F. Linder (Berlin): In view of the relatively minor changes in operative technique, the remarkable progress in surgery, which has been achieved during recent years, seems to be largely due to three factors. These are: (1) Improved methods of anæsthesia; (2) replacement of blood, fluids and electrolytes; (3) chemotherapy.

As a result, the operative risk in the commoner operations, e.g. gastrectomies, has been lowered, in spite of a higher average age of the patient. Furthermore, the development of a whole series of new operations, in the thorax, upon the heart and great vessels has been facilitated. These three factors, mainly due to Anglo-American medicine, have become effective in Germany only since the end of the Second World War. Since these factors became operative all over the world within a relatively short space of time, the evaluation of antibiotics alone is difficult.

In the fight against surgical infections chemotherapy has come close to a triumph. Colebrook in England was the first to treat streptococcal septicæmia successfully with the sulphonamides of Domagk. Penicillin, developed in this country, was the first effective weapon against staphylococci. To-day antibiotics have partially or completely replaced some operations, e.g. for early osteomyelitis, and in others they have reduced the risk of operation. But the antibiotics are not free from harmful side effects. As with all drugs, we differentiate three groups of reactions:

(1) *Toxic reactions*—which are avoidable by strict attention to dosage.

(2) *Allergic reactions* which, independent of dosage, can lead to anything from a mild skin reaction to death. In 1955 my colleague Goetze was able to collect 53 fatal reactions to penicillin alone, from the world literature.

(3) *The third group* comprises non-specific side effects, to which belongs the increase in resistant organisms. This has led to a breach in our antibiotic defence. Superinfection with resistant, or less resistant, organisms, has given rise not only to new therapeutic problems, but has unfortunately brought a threat to the life of many a patient.

I shall give some clinical pictures of resistant strains and superinfection as they occur in the daily practice of a general surgeon. I shall also discuss the indications for antibiotic therapy in surgery, since the indiscriminate use of antibiotics has led to the present state of affairs, making restrictions necessary.

A *survey of the surgical bacteriology* gathered from non-selected examinations of wounds, sputa, pleural aspirates and urine during the last four years in my clinic (Fig. 1) reveals the predominance of hæmolytic *Staphylococcus aureus*, whose resistant strains have set us new problems as everywhere else in the world. The part played by the hæmolytic streptococcus is infinitesimal in comparison; it has fortunately lost little of its sensitivity and therefore seems to be clinically benign. A larger section is made up of *Esch. coli*, proteus and pyocyaneus, which belong, as does the tubercle bacillus, to a group of organisms which respond only slowly or incompletely to chemotherapy and often become resistant. About 5% are due to *Candida albicans*, although this is only rarely a pathological finding, being mainly saprophytic; but if antibiotic therapy, especially with tetracyclines, is allowed to disturb the equilibrium of organisms, the living conditions of this fungus can be considerably improved. Best known are the ano-genital skin lesions.

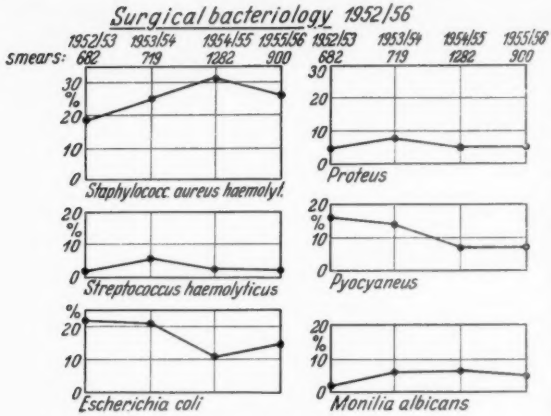


FIG. 1.

Rarer, but more serious, are internal, septicæmic *monilial infections*, which have been seen in practically every organ. We saw a single, severe case of pulmonary moniliasis in an adult, who had been treated for weeks with all available antibiotics as his pneumonia was slow to resolve. Rupture of bronchopneumonic monilial abscesses had led to bilateral pneumothorax. The cessation of all antibiotics and bilateral aspiration-drainage brought a gradual improvement of his serious condition.

The *existence of chronic anatomical lesions*, e.g. soft-tissue fistulæ, bone cavities, bronchiectasis, predisposes to the appearance of resistant organisms. The treatment of these lesions with antibiotics alone is useless in most cases. If the attempt is made, superinfection with resistant organisms is almost inevitable. A case based on a pinned and infected pseudarthrosis of the femur will illustrate this old story. The bacterial flora of this bony fistula was followed up for over two years. At first the staphylococcus showed a satisfactory sensitivity to penicillin. This was lost and the tetracyclines also failed in the end. The *Esch. coli* went through the same stages. Finally, *Proteus vulgaris* came along, often in pure culture and was soon resistant to all the then available antibiotics and sulphonamides. A cure was achieved only after it was possible to eradicate the focus of infection surgically. Another organism, which often perpetuates infection after prolonged antibiotic therapy is the *B. pyocyaneus*. After the destruction of the primary infecting agent, this saprophyte can become pathogenic and so maintain the infection—often in pure culture. A typical example can sometimes be observed after lung resections with consequent infection of the pleural cavity. In some cases this pyocyaneus infection can be cured by aspiration and instillation of polymyxin B only.

For the surgeon, the chief problem of bacterial resistance is presented by the behaviour of the hæmolytic *Staphylococcus aureus*. As is generally known, its resistance has rapidly increased all over the world parallel to the increase in antibiotic therapy. This development was delayed in Germany for obvious reasons. In Berlin penicillin was available in unlimited quantities only after the end of the blockade in 1949. Thereafter, our staphylococci also rapidly became adapted and by 1955 the sensitivity of staphylococci in our own clinic showed a resistance to penicillin and streptomycin in 72% and 60% of the strains tested. With tetracyclines, resistant strains were 33% approximately. With erythromycin (6%), neomycin (0%) and especially with the new oleandomycin (0% resistant strains) the position is still favourable at present. In 1956 the sensitivities to the usual antibiotics have remained unaltered, but the erythromycin-resistant strains have unexpectedly disappeared. We attribute this to our again more frequent use of chloramphenicol, so that erythromycin was used only as a last resort. The regression of bacterial resistance under antibiotic rotation-therapy appears as a ray of sunlight in the dark skies of this deplorable chapter.

Nowhere has the epidemiological significance of resistant staphylococcal strains been followed up more thoroughly or with more success than in this country. Authors like Blowers, Colebrook, Hare, Lowbury and Shooter, amongst others, have not only studied the ways of transmission of these germs in hospital, but have also given valuable advice on the prevention of this new plague. Fundamentally it is also our experience that the carrier rate amongst the new admissions rises from 30% to 70% within a few days, even when these patients have not received any antibiotics. The proportion of nasal carriers among our own personnel is shown in Fig. 2. Repeated examinations in 1956 showed a retrograde tendency, although, so far, no carriers have received local therapy. Perhaps this can be explained by a simultaneous decrease in the use of antibiotics, to which I shall refer later.

As a result of the ubiquitous presence of resistant staphylococci in hospital, endemic infections of the most varied localizations are known. First there are the *furunculoses of the skin*, which often cause more suffering to the patient than the initial operation itself. Also *post-operative parotitis*, which became quite unknown during the first years of anti-

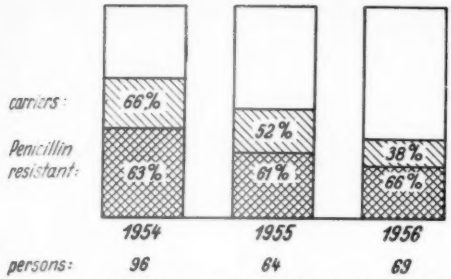


FIG. 2.—Nasal carriers of staphylococci amongst hospital staff, Chirurgische Klinik der Freien Universität Berlin.

biotic prophylaxis, is coming to the fore again. In the course of a single year we have observed 14 cases (0·8% of all operations). In the majority, hæmolytic staphylococci, always resistant to penicillin and often resistant to tetracyclines, were found either in the mouth or in the pus obtained from incision.

The local instillation of neomycin and bacitracin into the Stensen's duct of the inflamed gland has been of use only in the very early stages of the disease. Commonly we give parenteral or oral erythromycin and lately a combination of tetracycline with oleandomycin. In this way we hope to combat the resistant staphylococci and also the Gram-negative bacteria since we have had four cases with a pure culture of *Aerobacter aerogenes*. Naturally, according to a principle of chemotherapy, success can only be achieved if a sufficient concentration of the antibiotic reaches the site of infection before sequestration of the gland has taken place.

The same therapy has been successful in resistant *staphylococcal pneumonia*. We must bear this condition in mind whenever post-operative lung-infiltrations are slow to resolve. Not infrequently there is abscess-formation—as in a case we had after a mitral commissurotomy—which can, however, heal completely under conservative therapy. Another superinfection with resistant staphylococci is *pseudomembranous enterocolitis*. This clinical picture is not solely the result of antibiotic therapy, as it had been described, as far back as 1893, by Finney. Nevertheless, this syndrome, as a result of treatment with broad-spectrum antibiotics and sometimes also of parenteral penicillin and streptomycin therapy, has increased since its first description by Kramer in 1948. According to the simplified explanation of Poth, antibiotic therapy suppresses the normal intestinal flora, so that strains of staphylococci, usually acquired by cross-infection, can grow without hindrance and, through the release of their highly poisonous enterotoxin, produce this serious syndrome. In 1955 Senn collected 83 cases from the world literature, which surely represent only a fraction of the actual disaster. Therapy with erythromycin or oleandomycin, by replacement of fluids and electrolytes and with ACTH and noradrenaline can save only a small proportion of these cases.

A further serious consequence of the hospital strains of staphylococci seems to be the *increased rate of wound infections*, as reported so frankly from several clinics (Howe; Blowers; Shooter). Our own proportion, in 1956, of 2·9% minor and 2·9% severe infections surpasses what we were accustomed to in the pre-antibiotic era.

Table I shows the distribution of responsible organisms in 30 infected cases after aseptic

TABLE I.—SENSITIVITY OF ORGANISMS FOUND IN 30 WOUND INFECTIONS AFTER ASEPTIC OPERATIONS, 1956

Organism	No.	Sensitivity tests	Resistance to: Penicillin+ streptomycin	Tetracycline	Neomycin	Erythromycin	Polymyxin
Staphylococcus aureus	17	12	8	4	—	—	—
Staphylococcus albus	2	1	1	—	—	—	—
Streptococci							
(1) *β-hæmol. str.*	1	1	—	—	—	—	—
(2) *α-hæmol. str.*	1	1	—	—	—	—	—
(3) *Enterococcus*	3	2	1	1	—	—	—
(4) *Pneumococcus*	1	1	—	—	—	—	—
Escherichia coli	9	9	3	3	—	—	—
Proteus	2	2	1	2	—	—	—

operations, amongst which the staphylococcus accounted for over 50%. The signs of fever and local inflammation were inhibited in a considerable proportion by antibiotic prophylaxis.

So much for the present situation, which has given rise to serious problems in surgery also. For their solution several measures are required. First there are those directed against the

spread of resistant organisms in hospital, which have already been effectively applied in his country. The continual introduction of new antibiotics cannot lead to any fundamental change in the situation. Rather it would seem necessary to reduce the present extent of antibiotic therapy to reasonable proportions.

In this connexion, the following is a short survey of the surgical indications for antibiotic therapy, as gathered from the literature and personal experience. Fundamentally we can differentiate two types of antibiotic therapy: (1) The prophylactic, and (2) the curative indications. Since the results of the *curative group* can be more clearly evaluated, it is shown first in Table II.

TABLE II.—CURATIVE ADMINISTRATION OF ANTIBIOTICS

(1) Surgical infections
  (*a*) often without operation: erysipelas, anthrax, osteomyelitis, face furuncle, cellulitis
  (*b*) as adjunct to surgery: perforated appendicitis, perforated peptic ulcer
(2) Wound infections after trauma or surgery
(3) Pulmonary and extra-pulmonary tuberculosis
(4) Local administration (often combined with systemic administration):
  pyogenic joint infection, pleural empyema, osteomyelitis, contaminated wounds

There is no doubt that many surgical infections take a more favourable course with modern chemotherapy. Nevertheless the old dictum "ubi pus, ibi evacua" still holds good. Even now osteomyelitis has by no means become a medical disease. In perforation peritonitis chemotherapy has, in my opinion, proved of value. On the other hand, it is interesting that, in the treatment of chronic typhoid carriers, chloramphenicol has failed completely, in spite of a high sensitivity of the organisms, and in spite of such great success in the acute illness. The surgical removal of diseased gall-bladders, on the other hand, gives a cure rate of 90%, as prolonged follow-up of 130 cholecystectomized patients has shown in Berlin. In serious wound infections only, and after previous sensitivity tests, parenteral chemotherapy should be used.

Table III shows the indications for the *prophylactic use of antibiotics*. It is in this field above all others, that great restraint is essential, as in many hospitals often the greatest proportion of antibiotics is given for this reason.

TABLE III.—PROPHYLACTIC USE OF ANTIBIOTICS

(1) War wounds
(2) Special accidental wounds: compound fractures, skull base fractures, burns, &c.
(3) Aseptic operations of
  (*a*) brain, heart; on bones, joints, &c. (but no antibiotics for hernias, thyroidectomies, sympathectomies or breast amputations)
  (*b*) lung, œsophagus, cardia, stomach, colon, infected bile duct and genito-urinary tract
(4) Operations in contaminated areas: amputation of gangrenous leg, carcinoma of penis
(5) Emergency operations in patients with infection outside surgical illness

In gun-shot wounds prophylactic chemotherapy seems justified, because only rarely is complete excision of the wound possible. The position is different with excised and sutured accidental wounds, the healing rate of which cannot be significantly improved by local or parenteral administration of antibiotics. Nevertheless, antibiotic prophylaxis is justified in certain special injuries as shown in Table III. The most controversial group of antibiotic prophylaxis is provided by the aseptic operations. Two sub-groups must be distinguished: (*a*) The purely aseptic operations and (*b*) those operations in which, at some point, the interruption of asepsis is made probable, as by the cutting of a hollow organ.

In the large majority of purely aseptic operations, such as herniorrhaphies, thyroidectomies and so on, antibiotics are contra-indicated, as the number of wound infections cannot thereby be reduced. In cases with rheumatic or congenital heart lesions, we give penicillin post-operatively, so as to hold the streptococci in check. Neurosurgeons and orthopædic surgeons have practised a particularly generous prophylaxis in lengthy operations. To-day, as far as I know, this tendency is being reversed.

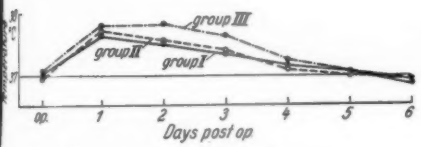
In lung resections we have, so far, given penicillin and streptomycin routinely (or we have been guided by pre-operative sensitivity tests) in order to prevent pulmonary or pleural infections. The danger of infection arising from a bronchial stump is, however, much smaller than expected, since bronchial swabs taken during operation for carcinoma or tuberculosis have proved to be sterile in 3 out of 4 cases. In surgery of the œsophagus and cardia, antibiotic prophylaxis has definitely reduced the danger of mediastinitis. Gastric resection, for peptic ulcer, is mostly a purely aseptic procedure. Through the action of acid

the stomach and first part of the duodenum or jejunum are sterile in 75% of cases. Therefore prophylaxis seems to be more indicated in cases of ulcerated and hypochlorhydric carcinoma of the stomach, in two-thirds of which our swabs have shown contamination with *Esch. coli*, staphylococcal or streptococcal organisms. On the other hand, gastric resections by the appropriate technique should provide no danger of contamination of the peritoneal cavity or of the abdominal wall.

Among operations on the colon, rectal amputations can be practically sterile from beginning to end. Therefore, only the resections with primary anastomosis make intestinal antisepsis desirable. We have tested all the drugs available for gut sterilization, including combinations of neomycin, and yet we still do not know if these drugs really produce better results than are achieved by a clean operative technique alone. Most antibiotics are excreted in high concentration in the bile and urine. They can therefore be used with success in the treatment of severe pericholecystitis, cholangitis or urinary tract infections. A simple cholecystectomy or nephrectomy obviously requires no prophylaxis.

Operations in infected, or previously infected, areas give an opportunity for specific prophylaxis, since, either before or during the operation, the sensitivity of the responsible organism can be tested. This field of application is not very big. Numerically the indications are even fewer in emergency operations on patients with a concurrent infection.

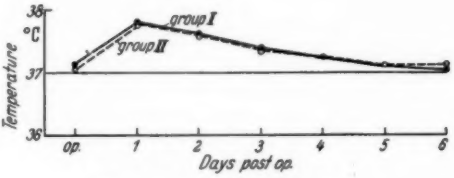
In order to test the value of prophylaxis in clean operations statistically, we have tried to compare identical groups of operations with and without antibiotics (penicillin and streptomycin post-operatively for five or six days). Such investigations are best done in a single clinic, since the selection of patients, operative technique and post-operative care, &c., can here be most easily compared.



Percentage of Wound Infections

	Severe	Mild	Total
Group I	1·2	5·3	6·5
Group II	—	5·6	5·6
Group III	5·0	5·0	10·0

FIG. 3.—Post-operative course of partial gastrectomies (benign ulcers). Group I: Prophylactic antibiotics, 170 cases, average age: 50·5 years. Group II: No antibiotics, 53 cases, average age: 50·4 years. Group III: Perforated ulcers with primary resection, average age: 48·3 years.



Percentage of Wound Infections

	Severe	Mild	Total
Group I	0·48	8·27	8·75
Group II	—	6·76	6·76

FIG. 4.—Post-operative course of cholecystectomies. Group I: 256 patients with antibiotic prophylaxis, average age 48·9 years. Group II: 59 patients without antibiotic prophylaxis, average age 50·2 years.

Fig. 3 shows the post-operative course of partial gastrectomy for peptic ulcer. The average evening temperatures of the test groups I and II are practically identical. Only in the group of primary resections for perforated ulcers (always treated with antibiotics) the temperatures lie higher. The number of wound infections in group II, which were not given antibiotics, was certainly not higher.

Results are similar with cholecystectomies. Here also neither the temperature chart nor the percentage of wound infections shows any advantage in antibiotic prophylaxis (Fig. 4).

Also other complications, such as bronchopneumonia or parotitis, are by no means rarer in patients who received post-operative prophylaxis. The figures are shown in Table IV.

TABLE IV.—COMPLICATIONS DURING POST-OPERATIVE COURSE
(Gastrectomies, Cholecystectomies, Thyroidectomies, Breast Amputations)
Group I: 621 patients with antibiotics
Group II: 158 patients without antibiotics

	Bronchopneumonias	Parotitis (gastrectomies and cholecystectomies only)
Group I	4·2%	1·85%
Group II	2·5%	1·69%

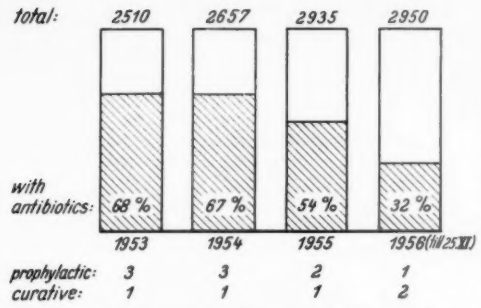


FIG. 5.—Rate of hospitalized patients who received antibiotics.

In our clinic we also have given antibiotics in abundance for a long time. It was not until the end of 1955 that we became more strict, due to the problems arising. The result of this policy is shown in Fig. 5. The total number of patients receiving antibiotics has lessened. The ratio of prophylactic to curative administrations has changed from 3 : 1 to 1 : 2 and will, I hope, sink still farther because even our residents have been convinced that this restriction is not only meant to cut down the expenses of the hospital.

In conclusion I would say that the value of chemotherapy in surgery is undoubted: but its indiscriminate use has created fresh problems. Asepsis has proved once more a fundamental principle in surgery for which chemotherapy—even partial—can never be a substitute.

Dr. R. A. Shooter: We have followed two types of infection in Professor L. P. Garrod's laboratory at St. Bartholomew's Hospital.

Treatment of Urinary Infections

Three years ago we carried out an investigation designed to see how well patients with urinary infections responded to chemotherapy, and how accurately laboratory tests of sensitivity to antibiotics forecast the eventual outcome of treatment (Garrod *et al.*, 1954). With the co-operation of the medical and surgical staff we collected records and examined specimens from nearly all the adult patients with urinary infections in or attending the hospital during eleven months. In uncomplicated infections there was good correlation between the cure rate and the guidance given by sensitivity tests, but for the series as a whole it was clear that what mattered primarily in the treatment of urinary infections was the condition of the patient's urinary tract. In the presence of stones or structural abnormalities or obstruction, the results were poor. Of the patients with abnormalities of this sort only 34% of males and 58% of females had sterile urine after treatment. On the other hand over 80% of the patients with no known abnormality and no previous history of urinary infection had sterile urine immediately after treatment. Between these two immediate cure rates was an interesting group composed of patients with no known abnormality, but with a history of previous infection.

I would like to put forward our experience with urinary infections as an example of resistance to treatment in which the patient is responsible rather than the resistant organism. An example of the other type of resistance, in which an infection is due to organisms resistant to the action of antibiotics, is provided by the present position with hospital staphylococci.

Staphylococcal Infections

Resistant staphylococci are resistant to penicillin because they form an enzyme, penicillinase, which destroys penicillin. One cannot make a staphylococcus resistant in this way to penicillin by exposing it to penicillin in the test tube or in the patient, and the resistant staphylococci which we now have in hospitals are the descendants, by selective breeding, of about 5% of pre-war strains. As a corollary to this, if a penicillin-resistant staphylococcus is isolated from an infection where before there was a sensitive staphylococcus, it nearly always represents the result of cross-infection by a new staphylococcus. With the enormous usage of penicillin there has been a steady climb within hospitals of the proportion of resistant staphylococci, and this is reflected in the number of resistant staphylococci isolated from out-patients. Table I shows the proportion of penicillin-resistant staphylococci which we have isolated from patients with septic lesions attending the out-patient department between 1949 and 1956. Patients attending other departments in the hospital were excluded and, whenever possible, swabs were taken at the first attendance or when the lesion was incised.

As opposed to penicillin, resistance to other antibiotics is the result of contact with the drug. Once acquired, resistance is permanent, and by cross-infection, these strains have multiplied to a serious level. Table II shows the results of tests done in our laboratory on staphylococci isolated from infections within the hospital in the last eighteen months. (Organisms from one ward with an epidemic have been excluded.)

TABLE I.—PATHOGENIC STAPHYLOCOCCI ISOLATED FROM OUT-PATIENTS

Date	Number of strains	Percentage resistant to penicillin
1949–50	261	6
1952	200	16
1954–55	200	21
1956	200	26

Based on Griffiths, E., Jones, P. F., Shooter, R. A., and Heady, J. A. (1949) ***Brit. med. J.***, ii, 958: Griffiths, E., Walker, A. J., and Shooter, R. A. (1950) ***Brit. med. J.***, i, 761: Birnstingl, M. A., Shooter, R. A., and Hunt, M. F. (1952) ***Brit. med. J.***, ii, 253: Rees, E. G., Shooter, R. A., and Shawe, G. D. H. (1955) ***Brit. med. J.***, i, 1409: Burn, J. I., Huntsman, R. G., and Shooter, R. A. (unpublished).

TABLE II.—ANTIBIOTIC SENSITIVITY OF STRAINS OF *Staph. pyogenes* ISOLATED DURING EIGHTEEN MONTHS FROM SEPSIS IN HOSPITAL IN-PATIENTS, AND THE PURCHASE OF ANTIBIOTICS IN THAT PERIOD AND THE PRECEDING FIFTEEN MONTHS

Sensitivity		Purchase of antibiotics (% of total) (by weight)	
731 strains	Percentage		Percentage
Resistant to penicillin	75	Penicillin	45
Resistant to tetracycline	23	Tetracyclines	35
130 strains			
Resistant to chloramphenicol	5	Chloramphenicol	1
Resistant to erythromycin	none	Erythromycin	1
		Streptomycin	18

So far, resistant strains have been dealt with by new antibiotics, and there are at the moment at least three promising new ones. Staphylococcal septicæmia is a possible exception to this generalization. This infection is sometimes accompanied by an endocarditis, and for the successful treatment of an endocarditis an antibiotic which kills, rather than one which only inhibits, bacterial growth is to be preferred. As yet we have no new antibiotic which can take the place of penicillin and streptomycin as killing agents, and one that could do so would be very welcome.

I would like here to discuss the way in which sensitivity tests are done. Nearly all those in common use determine if an antibiotic will inhibit the growth of an organism. There are several methods of finding this out. We have preferred one in which the sensitivity is determined in primary culture. One reason for choosing this method is that if a sensitivity report is delayed for three days it loses much of its practical value, and with the direct method a specimen can be received in the afternoon and a report sent the next morning. In cases of urgency, and if the infection is a heavy one, a good idea of the sensitivity may be obtained after as little as five hours' incubation. An additional advantage of this method is that it facilitates the recognition of infections due to mixtures of sensitive and resistant organisms.

Another way of looking at resistant organisms is to try to prevent their formation. For all antibiotics, the more they are used, the greater the risk of producing resistant strains, and conversely, with less use, fewer resistant strains are made. In support of this Table II shows purchases of antibiotics in two years and nine months together with the percentage of resistant strains of staphylococci isolated from in-patients.

There are two other aspects of staphylococcal infection I would like to consider. When I was adding up the staphylococci from in-patients, I made a separate record of those from infections of nurses (Table III). It showed what we have, unfortunately, known for some

TABLE III.—SENSITIVITY OF 64 STRAINS OF *Staph. pyogenes* FROM SEPTIC LESIONS OF NURSES

Sensitivity	Number of strains
Sensitive to penicillin and tetracycline	5
Resistant to penicillin, sensitive to tetracycline ..	57
Resistant to penicillin and tetracycline	2

time: that staphylococci isolated from septic lesions of nurses are likely to be resistant to penicillin. The most interesting observation was that only two nurses were infected with tetracycline-resistant staphylococci, although these organisms were not rare within the hospital. Many of our nurses are nasal carriers of strains of *Staph. pyogenes* resistant to penicillin but sensitive to tetracycline, and perhaps the tetracycline-sensitive strains can compete successfully with strains which are resistant.

One of the most alarming forms of staphylococcal infection is staphylococcal entero-colitis. This relatively new condition, which has to be differentiated from other causes of diarrhœa after operation, appears to be due to an invasion of the gut wall by staphylococci. Fig. 1 shows the bowel wall of a fatal case, the dark material just below the surface being composed of enormous numbers of staphylococci. Entero-colitis has been reported in patients treated with Terramycin, Aureomycin, tetracycline and penicillin and streptomycin used together. Why one patient and not another should develop it is not known, although the fact that nearly every reported case has followed the use of antibiotics which suppress bowel bacteria, suggests that these normal bacteria can suppress the growth of staphylococci or that when they are removed conditions become more suitable for staphylococci. In contrast with the broad spectrum antibiotics, penicillin is rapidly destroyed in the bowel, and, as far as I know, no case of entero-colitis has been reported after penicillin alone. We have seen some 30 cases of this new condition. Only one has died, on the third post-operative day, the others being arrested by treatment or being relatively mild infections.

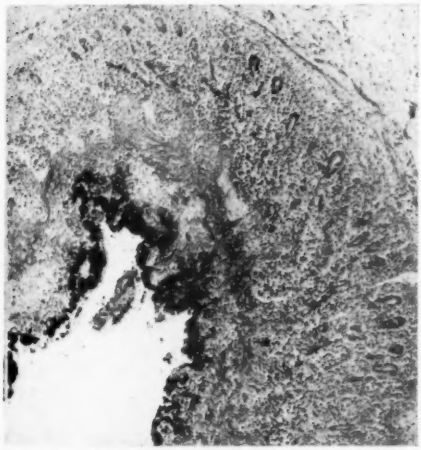


FIG. 1.—Section of jejunum showing superficial necrosis of mucosa. The dark-staining material on the mucosal surface consists of masses of staphylococci. ×50.

Photograph kindly lent by Dr. A. G. Stansfeld.

How to make the laboratory diagnosis is still uncertain. In our experience 30–40% of in-patients may carry pathogenic staphylococci in their stools, irrespective of treatment with antibiotics, and for this reason a culture may be misleading, as well as taking too long. So far, in our cases, we have relied on finding clusters of Gram-positive cocci in stained films of fæces, something we have only seen once in a large number of normal stools. There are reasons for suspecting that only a few types of staphylococci can cause enteritis, but even if this is so these types are now widespread, and in view of the rapidity with which patients may die, I think it is well worth while to make as a routine, stained films from patients with diarrhœa after broad spectrum antibiotics.

If the diagnosis is made in time, treatment is not difficult. It consists in stopping the offending antibiotic, restoring the fluid balance and removing the staphylococci with an antibiotic to which they are sensitive. At present this usually comes to the prescription of erythromycin, something which constitutes an additional reason for avoiding the use of this drug unless absolutely necessary. A new drug, or some new way of controlling the spread of staphylococci, might solve our problems rapidly. On the other hand, staphylococci have shown remarkable adaptability in the face of antibiotics, and have, so far, largely evaded attempts to control their spread, and I suspect that they will continue to present a major problem for some years to come.

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Section of the History of Medicine

President—DOUGLAS GUTHRIE, M.D., F.R.C.S.Ed., F.R.S.Ed.

[*December 5*, 1956]

The History of St. Peter's Hospital for Stone, London

By CUTHBERT E. DUKES, M.D., F.R.C.S.

ST. PETER'S HOSPITAL FOR STONE was founded in 1860, much later than most of the other special hospitals in London. The initial appeal for public support, dated March 12, 1860, declared that "there are in London six charitable Institutions for Idiots and Lunatics, nine for Lying-In Women, four for Women and Children, seven for Diseases of the Eye, two for Diseases of the Ear, four for Diseases of the Chest, two for Diseases of the Skin, five for Deformities, one for Cancer, one for Fistula, one for Fever, one Lock Hospital, and three Vaccine Institutions, yet there is no Hospital specially appropriated to the treatment of Stone". "Therefore", the appeal continued, "Some Noblemen and Gentlemen now propose to supply the existing want by founding an Hospital for the treatment of Patients labouring under Stone and other diseases of the urinary organs."

It was stated that one of the first objects of the proposed hospital would be to replace, as much as possible, existing operations of cutting for stone by newer methods designed for the crushing or dissolving of stones.

Another reason for establishing a special hospital for calculous disease of the urinary organs was provided by the fact that in the middle decades of the nineteenth century there had been a marked increase in the frequency of stone in England. According to the Registrar-General's reports, the number of deaths from stone and other diseases of the urinary organs had almost doubled in the ten years 1850–1860. It is difficult to explain this increase entirely on the grounds of more accurate diagnosis alone. Joly, J. S. (1940, *Med. Pr.*, **204**, 262) suggested that it might be an aftermath of the "hungry forties", just as the wave of calculous disease which swept over Central Europe in the 1920s was thought to be the result of privations during and after the First World War.

There are, of course, many different ætiological factors in the causation of calculous disease of the urinary organs. Some of these are of an individual or personal nature such as anatomical abnormalities, peculiarities in metabolism, urinary obstruction or infections; but if these are excluded the most obvious general factor responsible for calculous disease has always been a monotonous and unsatisfactory diet. It was formerly thought that stone in the kidney or bladder was due to over-indulgence in food. The exact opposite is the case. It is always commoner amongst poor people who are badly fed, and it declines in frequency when the diet is improved. The incidence of calculous disease has always been one of the most delicate indicators of dietary deficiency.

The Hospital for Stone, as it was first called, was opened in the autumn of 1860 at 42, Great Marylebone Street[1]. It was little more than an out-patient department as the building chosen was too small to accommodate more than a very few beds. The first

[1] The premises which in 1860 were No. 42, Great Marylebone Street were demolished in the early part of 1902. They were rebuilt (with No. 41) as shops and flats in 1903 and in 1904 an Order was made by the London County Council for the abolition of Great Marylebone Street and its incorporation with New Cavendish Street, with consequent renumbering. As the result of this, Nos. 41/42, Great Marylebone Street became No. 59, New Cavendish Street.

A further renumbering Order was made by the County Council in 1937, following the incorporation of Upper Marylebone Street, and as the result of this Order No. 59 became and is still known as No. 34, New Cavendish Street—three doors from the junction with Welbeck Street and occupied by Down Bros. and Mayer & Phelps Ltd., Surgical Instrument Makers.

Annual Report issued by the hospital tells us that the original intention had been to establish an in-patient department "in a healthy suburban situation", but this project fell to the ground from lack of funds. Three years later the committee secured the lease of 54, Berners Street[1], and in 1863 the hospital was moved there to a house large enough to accommodate 15 beds, though only about half of these were utilized at first in order to save expense.

When the hospital changed its address it also changed its name. As long as the institution had been in Great Marylebone Street it was called "The Hospital for Stone"; when it moved to Berners Street the name of "St. Peter's Hospital for Stone" was adopted. No reason or explanation for this change is to be found in the annual reports. In a short history of the Hospital published in 1940 Mr. Swift Joly pointed out that the custom of calling a hospital after some eminent saint has existed for several centuries and in many instances the result is appropriate and in good taste, but in a few it has been rather regrettable. He continues, "In no other instance does the name of the saint give an indication of the special work of the hospital."

During the first few years the Hospital for Stone met with even stronger opposition than had been experienced by the Eye Hospital at Moorfields which had been founded in the early years of the nineteenth century, by St. Mark's Hospital dating from 1835, by the Orthopædic Hospital in 1839, the Cancer Hospital (1851) and the Hospital for Sick Children (1852). This opposition found frequent expression in the *British Medical Journal*, which in its issue of June 16, 1860, launched a tirade against all the Special Hospitals of London. This was followed a few weeks later by a manifesto signed by many of the senior physicians and surgeons then on the staff of General Hospitals, beginning as follows: "We the undersigned are of opinion that much detriment to the public and to the medical profession arises from the modern practice of opening small institutions, under the name of hospitals, for particular forms of disease, in the treatment of which no other management, appliance or attention is required than is already supplied in the existing General Hospitals. . . . As an example that the evil referred to is increasing we regret to observe that an attempt is being made to set on foot a special hospital for the treatment of stone and diseases of the urinary organs. We desire to express our opinion that such an institution is especially unnecessary" (*Brit. med. J.*, 1860, ii, 582).

When St. Peter's moved to Berners Street the attack was renewed in another leading article in the *British Medical Journal* (1864, ii, 581), and in 1866 Mr. W. J. Coulson, a surgeon at St. Mary's Hospital, was called upon to resign his appointment at St. Mary's because he had accepted an appointment at this new special hospital (*Brit. med. J.*, 1866, ii, 703). But Mr. W. J. Coulson held the appointment of Surgeon to St. Peter's Hospital for twenty-five years, and at his death in 1890 the Committee recorded "that the present position of the hospital was due chiefly to his tact and affability which endeared him alike to the patients and his colleagues and all who had the privilege of working with him".

The many criticisms of Special Hospitals expressed in both the *British Medical Journal* and the *Lancet* during the early eighteen-sixties were not left unanswered, and the following extract from the Eighth Report of St. Peter's Hospital is a fair sample of the arguments in support of a Special hospital for Stone. This declared that "a leading journal has devoted several articles to prove that Special Hospitals are not only useless but injurious, but your Committee protest against sweeping assertions of this kind. Experience has abundantly proved that the only way of dealing successfully with the various types of disease that afflict humanity is to make each one the subject of particular study and care. It was with a view of alleviating the widespread suffering from Stone and other Urinary Diseases that St. Peter's Hospital was founded, and the friends of this Institution hope that their exertions may lead to as large an increase in the knowledge of these maladies, and to as great an improvement in their treatment as has been attained by the establishment of Special Hospitals for diseases of the Eye, the Chest, the Skin, the Throat, for Fever, for diseases of Women, and for Deformities" (Eighth Report of St. Peter's Hospital, 1868).

The accommodation in the Berners Street house was unsatisfactory and the work hampered by lack of funds until suddenly in 1873 the whole outlook was changed by an anonymous donation from a benefactor whose identity has never been divulged but whose generosity is commemorated by a brass plate in the hall of the present building. This tablet states the facts but gives no details.

On February 11, 1873, a stranger called at the hospital and presented a sealed packet to the Secretary. He demanded a receipt for it, at the same time stipulating that this packet should not be opened until he had left the building. The packet was found to

[1]Berners Street runs north to south from the Middlesex Hospital to Oxford Street, and No. 54 was situated on the west side about half-way down, but to-day you will look for it in vain.

Numbers 51, 52, 53, 55 and 56, Berners Street are occupied by the wallpaper merchants, Arthur Sanderson & Sons. No. 54 has ceased to exist.

contain ten thousand pounds—ten Bank of England notes for one thousand pounds each! The name of the donor was not disclosed, nor were any stipulations made as to the way in which the money should be spent.

The *British Medical Journal*, having lost the first round in its fight against St. Peter's, could not now resist the temptation of returning at once to the fray. Four days after the incident the Editor commented on it in the Editorial columns for February 15, 1873: "We understand that on Tuesday a gentleman called at St. Peter's Hospital for Stone, Berners Street, and left with the Secretary an anonymous donation of the sum of ten thousand pounds, in ten notes of one thousand pounds each. The munificence of the gift will attract deserved admiration. Wealth and munificence of this character involve, however, serious responsibilities; and on those who have at their command resources so extensive it must be considered an incumbent duty to watch over the useful administration of the funds which they provide. This institution is one . . . of the unnecessary special hospitals which constitute mischievous excrescences on our system of hospital charity; and the ill-advised munificence which endows it only tends to perpetuate an evil which might otherwise have been expected to die out with those who promoted it."

With this princely donation in hand the management committee began to look for better quarters and eventually found them in Henrietta Street, Covent Garden, to which address the hospital was moved in 1882. Here the newly built St. Peter's was formally opened by His Royal Highness Prince Leopold, Duke of Albany, on June 29, 1882. The total cost of the site and building was £13,923 and the furniture and incidental expenses £1,598, making £15,521 in all.

And now we come to the sequel of the story of the Anonymous Friend of St. Peter's, and one which gives it the authentic ring of the complete masterpiece.

In the year 1918 an old man was admitted to St. Peter's for prostatectomy. Before his operation he asked to see the Secretary, to whom he confided that he was the bearer of the envelope containing ten thousand pounds which had been left without any means of identification forty-five years previously. He explained that he was not the donor but that this "Friend of the Hospital" had died in the meantime. The name of the donor was confided to the Committee of Management. After a lengthy discussion in secret it was decided that since the donor had not revealed his identity during his lifetime and had apparently desired to remain anonymous, it would not be in accordance with his wishes to publish his name after his death. So no note of this discussion was made in the Minute book, and the name of this "Friend of the Hospital" is now lost for ever.

During the first forty years of its existence St. Peter's Hospital gradually built up a reputation for the successful treatment of stone in the bladder. The number of cases treated annually steadily increased and at the same time the death-rate after operation declined, attributable mainly to the substitution of litholapaxy for the former methods of operating, a procedure introduced by Bigelow of Boston in 1878. His operation consisted both in crushing the stone completely and evacuating the fragments from the bladder. As evidence of the change this brought about in the treatment of stone Swift Joly quotes a few figures from the statistics of St. Peter's Hospital. In the decade 1864–1873 the mortality following lithotrity (i.e. crushing the stone) was 15·25%. The average stay in hospital was about 100 days. In the decade 1915–1924 the mortality following litholapaxy (i.e. evacuation of the crushed stone) was 2·2%, and the patients only remained on an average five days in hospital. Bigelow's operation, combined with antiseptic methods, had brought about this striking change (Joly, J. S., 1929, Stone and Calculous Disease of the Urinary Organs". London, pp. 26, 27).

For the first forty years of its existence St. Peter's Hospital was true to its name and primarily renowned for the treatment of stone. When vacancies occurred on the staff preference was given to surgeons with special experience of calculous disease as shown by the fact that when in April 1896 the Medical Committee recommended that an additional Surgeon should be appointed to assist in the Out-patient Department the post was offered to Mr. P. J. Freyer (later Sir Peter Freyer) who, the report says, had "had considerable experience of calculous diseases in India".

Over four years later, in December 1900, Freyer performed his first suprapubic prostatectomy operation at the hospital. This operation revolutionized the general treatment of prostatic obstruction and also changed the emphasis of the surgical work of St. Peter's. There has been much controversy concerning the question whether or not Freyer was the first surgeon to carry out suprapubic prostatectomy successfully, but whatever views may be held about this no one will deny that by his teaching and example he effected a great improvement in the surgical treatment of prostatic obstruction, and greatly added to the renown of St. Peter's.

Freyer's operation held the field in Britain for twenty-five years. It was the operation of choice for the general surgeon, though few achieved results comparable with those

reported by Freyer. Many improvements were introduced a few years later by Sir John Thomson-Walker.

When St. Peter's Hospital was first built in Henrietta Street the ground floor at street level was rented to shops, but as the demand for beds increased the shops were displaced and the hospital came to occupy the whole site. The process of expansion and infiltration was a gradual one but by 1930 the entire building had been remodelled and a new out-patient department had been constructed on the ground floor, whilst the remainder of the available space had been used for an X-ray department and secretarial offices. There being no room for further expansion on the north side of Henrietta Street a house was acquired on the south side immediately opposite to the hospital, and here provision was made for the pathology laboratory, museum and Nurses' Home. This building, No. 10, Henrietta Street, is now the home of the Institute of Urology.

I think it is true to say that the Institute of Urology had its origin in a series of discussions between Sir Francis Fraser and Mr. Clifford Morson which took place early in 1946 at which it was agreed that steps should be taken first to unite St. Peter's Hospital with the neighbouring urological hospital, St. Paul's in Endell Street, after which the question of establishing an Institute of Urology could be considered. This proposal was submitted to the two hospitals concerned who agreed to commence organized instruction to post-graduate students early in 1947. Mr. Clifford Morson was subsequently appointed Director of Studies in the new Institute in May 1948.

All those of us who worked in the old voluntary hospitals before they were nationalized know how much these owed to the devoted services of members of the Committees of Management. Two names will long be remembered at St. Peter's. The first is that of Mr. F. A. Bevan who became Treasurer in 1866 and held this position until his death over forty years later. The second is that of Mr. Edwin Fox. He joined the Board of Management in 1879 and became chairman some twelve years later. He continued to hold this office until he died in 1933. To commemorate his long service to the hospital the paying ward which was opened in 1932 was named after him.

The History of St. Paul's Hospital, London

By A. R. C. Higham, F.R.C.S.

The tale I have to tell is not so exciting as that of St. Peter's; it lacks the highlights and some of the glory, but it is a story of humble beginnings, of difficulties overcome, of grave disappointments when success seemed at hand, of apparently inevitable ruin, and of final achievement that must warm the hearts of those still with us who knew the days of struggle.

A Mr. Felix Vinrace was the real father of the hospital: he interested a number of influential and philanthropic gentlemen, who met on May 27, 1897, "to consider the desirability of founding a hospital in Central London for the treatment of the many forms of skin and cognate diseases so prevalent in our midst".

A site was chosen, 13a Red Lion Square, and negotiations for the lease were concluded on March 24, 1898.

The large inscription in front "For Skin and Genito-Urinary Diseases" caused grave concern to certain residents in the Square; indeed, one, a Member of Parliament, was so incensed at the indecency of this inscription that he threatened legal proceedings. The Governors were unmoved.

The building was "replete with every accommodation befitting a modern hospital, embracing, obviously, its lighting throughout by electricity". Mr. Vinrace named the hospital "St. Paul's". He afterwards wrote "I spent some hundreds of pounds in putting the building into habitable repair—furnished it—and later on bought the lease which I now (1918) hold".

In view of what has since been written about the Patron Saint of our hospital, it is interesting to note that he said, in 1917—"The Committee have adopted one of the emblems of their Patron Saint as the Common Seal of the Hospital, as illustrated on the cover of this Report". This is the sword of St. Paul the Apostle.

The hospital opened its doors to its suppliants for relief on August 15, 1898, with Mr. Felix Vinrace, M.D., F.R.C.S., as Senior Honorary Surgeon, and Mr. Alfred Allport, M.R.C.S., as Assistant Honorary Surgeon (he was soon afterwards promoted to a "full surgeoncy"). There were 6 beds for in-patients.

The total Ordinary Income for the year ending December 31, 1898, was £76 19s. 6d. (there was a "loan" of £384 4s. 6d. Annual subscriptions amounted to £9 9s. 0d. There were donations of £32 16s. 0d., and the poor patients subscribed £34 4s. 6d. "Sale of Bottles" made 10s.

Expenses are interesting items: Provisions £3 7s. 7½d. Rates and taxes £6 13s. 0d. Nursing salaries £1 2s. 6d.

Throughout the early history of the hospital one is surprised to find what large sums were realized by the boxes in the hospital into which anonymous payments were made. In many years they amounted to more than the subscriptions of the well-to-do—and we had some of those, too: Horatio Bottomley gave us £10 0s. 0d., once.

In the first complete year's work there were 1,142 new cases, and 7,100 attendances. "As to the success of the treatment he could only say that of 16 operations performed during the past year (1891) not one had terminated fatally" (Annual Report, 1898–99).

I must interject here that I have seen the man who underwent the first operation in the hospital at Red Lion Square. He had had a wart on the penis treated then; I had to remove the whole organ for an extensive carcinoma at his second visit, sixty-three years later.

There is extant an interesting list of the places whence the patients came—London boroughs first, then the provinces. Among the list, but at the end, is one solitary entry from New York, U.S.A.

The South African War broke out and income dwindled, but enormous efforts were made—it was not unknown for the medical staff to have to put their hands into their pockets at the end of the week to find money to pay the orderlies, as one of them has told me. In 1904 donations amounted to £70 and patients' voluntary contributions to £441. In this year the Secretary defaulted to the tune of some £235 5s. 6d., and died in King's College Hospital, then, of course, quite near, while the Public Prosecutor was still considering *his* next step.

Debts now amounted to £2,037 11s. 10d. and assets to £114 5s. 1d. Nevertheless, patients continued to pour in, and the Surgical Staff was now four, with two anæsthetists.

By 1913 the income began to rise above expenditure, but there was a debt of £2,400. In-patients had had to be limited to 26 of the most urgent cases. The Insurance Act began to be a trouble: donations fell to £72 10s. 6d., while patients' voluntary contributions went up to £615 3s. 3d. Treatment with "606" was a great expense, X-rays were first mooted in 1913—it was thought that £150 would be required.

Then another war broke out, and the hospital had to be reorganized again. In 1916 St. Paul's became one of the 22 selected London Hospitals to give free secret treatment for V.D. In this year, 20 in-patients were treated for skin diseases and 606 for venereal diseases—this gives the first information of the incidence of the "cognate diseases" coyly mentioned in 1898; there were 20,000 attendances as out-patients, and new premises had to be found. An Extension Fund was opened, and in 1919 the present hospital site, then known as the British Lying-in Hospital was acquired for £15,000. This entailed a personal guarantee by the members of the Committee of Management—no small act of gallantry, which was soon to be tested. In 1921 the overdraft was £20,000, and all work on the new hospital had to be held up. At this moment F. N. Pickett endowed a laboratory, later to be known as the Pickett-Thomson Laboratory, which was built on the top floor of Endell Street. Dr. Robert Thomson began an association with the hospital which was only recently broken by his retirement. His brother David Thomson was the Director, and Sir Ronald Ross the President, of the laboratory, which was autonomous.

Finance continued to be the great difficulty, and the Hospital did not open up in Endell Street until 1923. It closed on Saturday, April 7, in Red Lion Square, and opened on Monday, April 9, at Endell Street "without friction".

In the first complete year at Endell Street out-patient attendances were 65,260 as against 20,168 in the previous complete year at Red Lion Square. It was obvious that the Medical Staff would have to be increased and the following appointments were made in 1924.

Claude H. Mills (Assistant Surgeon, 1914) and Graves Stoker were promoted Honorary Surgeons.

Kenneth Walker was made an Honorary Surgeon.

Sir Thomas Carey Evans, Winsbury White, and W. K. Irwin, Honorary Assistant Surgeons.

In 1926 the lift was installed, a Cystoscopy Room was equipped and opened, and post-graduate training in urology began.

That year saw a mortgage substituted for the system by which the members of the committee of management were individually responsible for the overdraft, and the medical staff was augmented by

Frank Kidd		
Jocelyn Swan	as Honorary	Consulting Surgeons
Nathan Mutch	,,	Physician
W. J. O'Donovan	,,	,, to the Skin Department
Frank Cook	,,	Gynæcologist

In 1927 the title of the Hospital was changed to "St. Paul's Hospital for Diseases (including Cancer) of the Genito-Urinary organs and Skin". This, after thirty years' activity, marked the change from the "cognate diseases" to Urology.

In this year the Ward was opened with 18 beds: an operating theatre was equipped and used (this is *still* in use) and an X-ray department was equipped at a cost of £2,000, the bulk subscribed through the exertions of the medical staff.

In this year also, Felix Vinrace died, leaving, as a final donation, the sum of £833 15s. 11d. to the Hospital—this was the money he had lent to the Hospital in its early days.

His recorded gifts to the hospital amount to nearly a thousand pounds: besides this he had persuaded many more than the few original "influential and philanthropic gentlemen" to give unsparingly of their time and treasure to set the Hospital on its feet.

He was born in 1858, was educated in Birmingham and at Queen's College, Galway; he studied medicine at University College and the London Hospital, qualifying as M.R.C.S. in 1879 aged 21. He became M.D. in 1881 and F.R.C.S. in 1886.

He was medical officer to the Hospital for Women in Soho, demonstrator of anatomy at the London Hospital, and had held posts as house surgeon, house physician and resident obstetrician at several Birmingham hospitals.

In 1887 he joined the Honorary Staff of the Birmingham Skin and Urinary Hospital, a post he held until 1919, being elected Consulting Surgeon in 1921. He must have spent a good deal of time in travel.

Between 1927 and 1930 the Honorary Staff was increased. Another gynæcologist, Alexander Galletly, a radiologist, G. R. Mather Cordiner, a cardiologist, T. Jenner Hoskin, and a surgeon in charge of the radium department, Stanford Cade, though it was not until the next year that £500 worth of radium was acquired.

In 1930 another great change took place. A separate department of venereal diseases was opened under the direction of Claude H. Mills, with Alfred Allport as his Assistant Director. The activities of the hospital and of this department have gone on side by side ever since, though they have been under separate management since 1942.

The next years were marked by steady development and the financial position gave less anxiety, though more hard work was required. In 1936 the hospital opened its own pathological laboratory.

In 1939 another reconstruction of the staff occurred, and three honorary assistant surgeons were appointed. They did not have time to arrange their out-patient days, let alone any operating sessions, before they were all in the R.A.M.C. and it was thought necessary to close the hospital for the great evacuation. However, before the year was out, it had to be reopened owing to popular demand, and it continued to work under the well-known difficulties with only one bad "near miss", in 1944, until the full reopening in 1946.

It was clear that great changes in the structure of the Hospital Services were imminent. The Governors entreated the other great genito-urinary hospitals to amalgamate with a view to building a centre of teaching and research—St. Peter's finally agreed, but All Saints remained outside, and so the Institute of Urology was originally based on St. Peter's and St. Paul's, which had amalgamated on May 9, 1948, without outside help.

I cannot conclude without paying a tribute to the original staff—men like Vinrace, Alfred Allport, who died in May 1949 and is commemorated in the ward of his name, Claude H. Mills, who taught me so much, Carey Evans, Winsbury-White and W. K. Irwin. These men not only worked in their own departments and did much of the day-to-day administration, but subscribed most liberally when funds were so vital, in the earlier days. Their recorded donations amount to over £8,500 and their unrecorded gifts must be very much more.

But, to us who remain, their greatest gift has been the example they left to us—we will not forget them. I wish to thank this Section for giving me an opportunity of making my sense of gratitude more widely known.

Section of General Practice

President—JOHN H. HUNT, M.A., D.M.

[*November* 21, 1956]

DISCUSSION ON CATARRH AND ITS TREATMENT

Dr. Harold Bloom:

Catarrh as a Family Illness

CATARRH is ubiquitous in the Western hemisphere. By long usage, the term has been applied both to the symptoms and to the exudates.

MORBIDITY IN CHILDREN

Enlargement of lymphoid tissue.—The constant, and often copious, mucopurulent discharges which occlude the nasal passages of certain "catarrhal" children must originate from large expanses of inflamed mucosa in the accessory sinuses.

Furthermore, the idea of "physiological enlargement of lymphoid tissue" is recognized to be a contradiction in terms. Any permanent enlargement of lymphoid tissue, whether subepithelial, or of tonsils, adenoids, nasal mucosa or cervical glands must be regarded as the result of inflammatory reaction to constant organismal invasion. This enlargement becomes evident in the pharynx after the first year of life, and its continued presence leads me to look for the source of the infection in the child's environment.

The common cold.—The common cold, or upper respiratory infection, is by far the most prevalent family illness known to us. It is highly infective and contagious, and is recognized by universal clinical and lay experience as a source of serious illness in young and old alike. The ubiquitous sequel to repeated infections is spoken of as chronic catarrh, which is constantly present in a large proportion of homes.

Now let us enquire into the effects upon the children of these repeated infections and of their aftermath.

Sources of infection in the home.—Douglas (1951*b*) found that, in all social classes, age or birth order, children are much more likely to suffer from respiratory infections when one or more of the other members of the family have frequent colds.

In another survey (1951*a*) he found that approximately 1 in 5 of children under 5 were admitted to hospital at least once. A small number went to hospital more than once. Readmissions occurred usually soon after the previous admission, and for the same cause, usually respiratory infection. These findings, if confirmed, suggest that the illness is the result of a source of constant infection or reinfection in the home.

The corollary to this situation is sometimes encountered. Children living in a home which harbours a chronic bronchitic repeatedly suffer severe respiratory infections. Soon after the death of the chronic invalid the children cease to be seriously ill.

We may infer from these surveys that there exist in the home two distinct sources of infection to children: (i) the intermittent colds, and (ii) a constantly present focus or foci. This last source is the individual with chronic catarrh.

THE CATARRHAL STATE

Catarrh in the adult.—The symptoms in the catarrhal adult, with his frequent and prolonged coughs and colds, stuffy nose and morning phlegm, are those of intermittent obstruction with retention and overflow in the upper respiratory tract. These symptoms have become part of the national heritage. Our patients, with their limited vocabularies, are unable to express themselves adequately. If the symptoms were brought to medical notice, the patients were often advised to ignore them (Ellis, 1954).

The signs invariably reveal the presence of long-standing and repeated inflammation in the respiratory tract. A brown pigmentation of the skin is often seen round the eyes outlining the orbits. The tongue is always coated, and often slimy. The pharynx and uvula are dusky, œdematous and often the seat of a granular hypertrophy of the subepithelial lymphoid tissue. Punctate hæmorrhages or dilated capillaries may be present

on the uvula, soft palate or tonsillar folds. Rivulets of mucopus, or even a frank cascade, may be seen, and sometimes mucopus wells up in the pharynx when the tongue is depressed.

In the nose the inferior turbinates are hypertrophied, œdematous and frequently obstruct the airway. Polypi may be present. The external auditory meatus is often the seat of a diffuse, indolent inflammatory process which sometimes reaches a focus in a meatal boil. The strictly healthy ear-drum is seldom seen in such families. It presents varying degrees of irregular thickening, retraction, scarring, plaque formation and often patchy œdema. No two drums show identical changes. Sometimes an indolent otitis media will produce a perforation and a heaping up of masses of unhealthy desquamation over the drum and meatus.

These signs are seen concurrently in the throat, nose and ears. They are the signs of chronic low-grade inflammation in the whole expanse of the respiratory tract. Somewhere within this a focus of chronic infection has developed and this may be demonstrated.

A radiological investigation in my practice confirmed the presence of this focus. During 1954, 22 out of 37 unselected catarrhal adults were found to have severe infection, hitherto undiscovered, in at least one paranasal cavity.

Catarrh in childhood and infancy.—Illingworth (1953), in assessing the health of the individual child, considers that the most important criteria of well-being are energy, happiness, freedom from infection and freedom from lassitude. In sharp contrast to this picture is the catarrhal child with his physical and mental lethargy. In between his attacks of illness he suffers from a condition of subclinical ill-health.

A familiar sign in the catarrhal child is a bluish shadowing round and under the eyes outlining the orbit. He toys with his food, drooping over table or desk and leaning on his elbows. He is round-shouldered, often has a lordosis with "winged" scapulæ, and the abdomen is frequently protuberant and tympanitic.

After the age of 1 year, when the effects of constant organismal infection are beginning to show macroscopic signs, physical examination reveals a picture similar to that seen in the adult. The tonsils and cervical glands are relatively much larger and the signs of fibrosis in the ear-drum and elsewhere are less advanced.

Catarrh in the baby.—The symptoms of infection of, and obstruction in, the upper respiratory passages in the baby are often dismissed as "snuffles". Snuffles in the newborn is described by Apley *et al.* (1954) as occurring in one in forty babies born in hospital. They found that the incidence rises steeply in the presence of a coryza infection among the nursing staff, and concluded that snuffles is an infection of unknown ætiology.

The symptomatology is similar to that of catarrhal infants and children. Its behaviour in the presence of "coryza" is similar to the familiar outbreaks of colds in the home. I believe, therefore, that snuffles is the earliest manifestation of the catarrhal state.

Sources of infection in the home.—Notwithstanding the assertion of Watson (1955) that the catarrhal state is a temporary condition, we see here clinical evidence of a permanent state of respiratory mucosal and lymphatic tissue reaction to constant organismal invasion. This reaction is abundant, prolonged and chronic, beginning as snuffles in the baby and progressing throughout life at varying levels of activity.

A focus of infection soon develops somewhere within the respiratory tract. These foci have been labelled chronic bronchitis or chronic otitis media, according to their position, and are well established by the time they are radiologically evident. The constant overflow into the pharynx from these foci is appreciated as catarrh.

These exudates constantly reinfect the pharynx and its lymphatic drainage.

In addition to this autogenous source of infection, there is the constant reaction to organismal invasion from other catarrhal foci in the environment. The catarrhal state thus behaves as a family infestation.

The acute exacerbations of inflammation, with retention and overflow, in this great area of respiratory mucosa are dismissed as "colds". The extensions of the colds are known as acute respiratory infections.

This thesis is supported by an investigation in my practice of the incidence of respiratory illnesses in the under-fives, and of the occurrence in their environment of chronic infection.

The Catarrhal Family

The observation that certain children appear to be more prone to illness than others led to the recognition of the catarrhal family, as distinct from the non-catarrhal family, which appeared to be analogous to the farm-worker's family mentioned by Douglas (1951).

The catarrhal family was defined as one in which a child, or children, suffered two or more attacks annually of acute upper respiratory, or pulmonary, infection, acute otitis media, or acute cervical adenitis, for which medical advice is sought. The definition is based upon observation or recorded knowledge of the family for at least two years.

Method of Investigation

All those families in my practice containing children born after December 31, 1949, were chosen. Children belonging to catarrhal families, according to the definition, were compared with the remainder. There were 107 catarrhal families with 136 children under 5, as against 20 non-catarrhal families with 25 children.

The incidence of acute respiratory illnesses in the children was recorded, together with the occurrence in their families of catarrh, chronic sinusitis, chronic bronchitis and chronic otitis media. A separate analysis was made for the presence in the family unit of the so-called "allergic" illnesses of hay-fever, migraine and asthma. Neither the severity nor the duration of the illnesses has been recorded.

Respiratory infections in children.—Table I shows that, in catarrhal families, there are four times more acute respiratory illnesses in the under-fives, than in non-catarrhal families.

Table I.—Incidence of Respiratory Infections in the Under-Fives

	Catarrhal families	Non-catarrhal families
Number of families	107	20
Number of under-fives	136	25
Total number of acute infections in under-fives	1,180	51
Number of child/years	408	69
Acute infections/child/year	2·9 (a)	0·7 (b)
Ratio of (a)/(b)	4·1/1	

Snuffles.—The analogy of snuffles to the respiratory infections was confirmed by this investigation. It was found that snuffles occurred four times more often in the babies of catarrhal than of non-catarrhal families.

The chronic respiratory illnesses.—A similar comparison showed that each of the chronic respiratory illnesses in the environment appears to cause more than four times as many episodes of respiratory illness in the children of catarrhal than of non-catarrhal families. Each of these chronic conditions may therefore be regarded as equivalent.

The "family" illnesses.—It was interesting and significant to find that each of the so-called allergic "family" illnesses appeared to cause four times more respiratory infections in the children of catarrhal than of non-catarrhal families. These conditions therefore appear to behave as infections of the same order as chronic bronchitis, and presumably as infections of the droplet type. Recent work by Brockbank (1955) and Russell (1955) supports this assumption.

Catarrh as a family illness.—This investigation showed that if there are two or more members of the family with catarrh, the under-fives suffer a disproportionate amount of illness (Fig. 1).

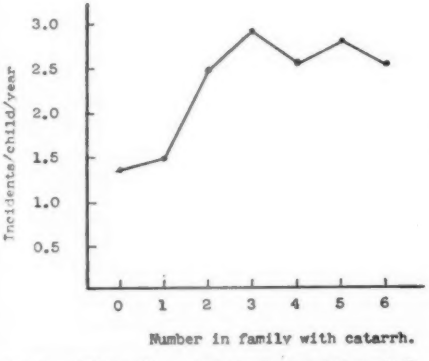


Fig. 1.—All families. Effect of catarrhal "units" in the home.

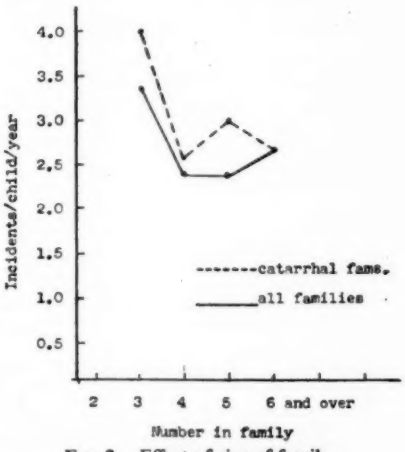


Fig. 2.—Effect of size of family.

The large family is no less healthy than the smaller one, so long as it contains no catarrhal "units". The only child appears to be a problem on his own, particularly in catarrhal families (Fig. 2).

Sources of infection in the home.—This investigation supports the clinical evidence that the chronic respiratory conditions, and the so-called "allergic" illnesses, behave as equivalent foci of droplet infection to children. Catarrh is the ubiquitous symptom of all these conditions, and appears as a family illness.

Discussion

I believe that one of the principal factors in the incidence and spread of the acute respiratory infections is the permanent slowing down, and ultimate partial paralysis, of ciliary action by the catarrhal exudates, and the consequent arrest of pathogenic organisms in them.

These catarrhal exudates are a medium highly favourable to the proliferation, and the spread, of the causal organisms of acute respiratory illnesses.

The total capacity of the air-spaces of the skull is stated to be 138 c.c. (Gray's Anatomy, 1955), or one cupful. In the upright position the overflow from these spaces is directed backwards into the nasopharynx. To this is added the overflow from the remainder of the respiratory tract. After stimulating salivation (Wright, 1952), the total mass is swallowed.

It would be well to consider the possible immediate and remote effects of the ingestion of this constant flow of mucopus, both in the acute and the chronic phases of the inflection.

Among the factors which aggravate the catarrhal state are atmospheric pollution, cold, sudden changes of temperature, humidity, fog, smog, tobacco smoke and damp housing conditions.

The emotional factor in catarrh cannot be ignored. Respiratory congestion resulting from emotional causes may precipitate a state of retention in which secondary organismal infection supervenes, producing the attack of asthma or sinusitis.

Within the limits of my practice, chronic otitis media, chronic bronchitis, migraine and asthma do not occur in non-catarrhal families. It is possible that our most catarrhal children grow up to become our chronic bronchitics and asthmatics. The approach to these conditions lies in the elimination of family catarrhal infestations.

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Dr. Guy Daynes:

Treatment of Catarrh by Warmth at Night (Abridged)

Warmth in various forms has been accepted as a standard treatment for inflammatory conditions of the upper respiratory tract for many years. Why then are catarrhal patients allowed to sleep in bedrooms with icy blasts of fresh air blowing in through the open windows? Unthinking tradition must be the answer to this question; window-opening whatever the weather began as a preventive treatment for tuberculosis and its success led to its adoption as a health rule throughout this country. Our belief in the almost magical properties of fresh air has continued unshaken ever since!

This health habit is now challenged and the suggestion is made that *catarrhal patients benefit by shutting their windows at night!* Very many cases of "catarrh" originate from chronic virus infections in the upper respiratory tract and antibiotic therapy is useless against these viruses; therefore reliance must be made on Nature's own mechanism of leucocyte defence. If mucous membrane capillaries are contracted by cold air, there will

be a smaller blood flow and fewer leucocytes will reach the attacking viruses and therefore defence will be less efficient. If, on the other hand, the capillaries are dilated by warmth, more leucocytes will be able to join battle with the viruses, thereby improving the position. Any good that can be done by warmth will be completely neutralized by the use of vaso-constrictor nose drops and these should be reserved for purely allergic catarrh. Though such drops may temporarily prevent catarrh formation (just as cold air can), the viruses, if present, will be able to enter the mucous membrane cells relatively unopposed, and catarrh will be worse later.

Catarrhal patients ought to remain in warm rooms, the temperature of which should not fall below about 60° F. This will mean having a source of heat of some sort in the bedroom on cold nights, in addition to a closed, or nearly closed, window. Care must be taken to maintain some ventilation so that the room is not stuffy. The only difficulty in using this simple therapy lies in overcoming the patients' prejudices against it. If resistance is encountered, patients can be compared to a man who, having a bad "cold", sits wearing two overcoats on a frosty day in a room without heating and with the window wide open! He may insist that he is perfectly warm, but is he being sensible? Most patients will say that he is either mad or determined to get pneumonia, whereupon it can be pointed out that they are doing precisely the same thing each night when they tuck themselves up in bed, having thrown open the window wide. Logic will usually persuade them to shut their window and stay in the warm, if their catarrh is troublesome enough to justify such a supreme sacrifice!

Dr. H. C. Faulkner:

Displacement Therapy in Nasal Catarrh. Brief Interim Report on the Use of the Proetz Displacement Technique in General Practice

The Proetz technique has been fully described by Bedford Russell.[1]

The ætiology of chronic nasal congestion is multifactorial. Anatomical structure, sensitivity to inhalants, changes of temperature and humidity in the atmosphere, smoking, infections, both of the nose and sinuses and the teeth and alveolar margins, and stress and emotion all can play a part. Some would add the repeated use of vaso-constrictor sprays and drops to the list. Persistent rhinorrhœa, particularly in children, may be little more than inconvenient. The headache and general malaise arise when the ostia of the sinuses are blocked. Possibly the air in the sinuses is absorbed and produces a temporary vacuum, which alone produces a "sinus headache". The fact that retained secretion can cause headaches even if not manifestly secondarily infected can be demonstrated by the relief obtained by drainage.

Diagnosis is relatively simple. A bull's eye lantern and a head mirror make examination far easier. Dental abscess or alveolar osteitis should be excluded. I have recently seen a patient who had extensive investigations of her sinuses and innumerable treatments before the dental cause was found. The nasal mucosa typically loses its pale pink normal appearance and is œdematous and injected. Tenderness over the frontal and maxillary sinuses is less reliable, and its absence does not exclude the condition.

Bacteriology is seldom conclusive; antibiotics, surgery (except in the acute or chronic case with pus under tension), and desensitizing injections, have been disappointing. A change of climate is often more successful, but available to few patients.

The Proetz method, first described by Proetz in 1931, and popularized by Bedford Russell to a limited extent in this country, is extremely simple and worthy of a trial in general practice.

The first requirement is a spray with a fine nozzle and a sufficiently long tube to go far back in the nose. Neophryn shrinks the mucous membrane more efficiently than ephedrine. The only other requirement is a rubber bulb, with a removable glass nozzle which fits tightly in the nostril. The nose is sprayed with Neophryn. A few minutes later the patient lies on a couch with the head over the end, with the chin and external auditory meatus in vertical alignment. Two drachms of normal saline containing ½% ephedrine hydrochloride are introduced, 1 drachm in each nostril, the patient breathing through the mouth. The bulb is then compressed and fitted snugly into one nostril. The patient repeats "key, key" while the bulb is allowed to expand gently. If the ostia are patent this allows air to leave the sinuses and some of the solution to enter. This is repeated a few times.

Of some 30 cases of chronic nasal catarrh treated this year, I have kept separate records of 12. All have had relief, some dramatic. One did not return after the second treatment when some relief was admitted. The 2 who do their own treatments have had several attacks during the year, but still find the treatment effectively obtains rapid drainage.

[1]Russell, H. G. B. (1955) *Med. World, Lond.*, **82**, 569.

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Section of Ophthalmology

President—R. C. DAVENPORT, F.R.C.S.

[*December* 13, 1956]

DISCUSSION ON THE VISUAL PROBLEMS OF NIGHT DRIVING

Mr. L. H. Savin (King's College Hospital, London):

The subject of this discussion raises among others the following problems for the ophthalmologist:

(*a*) *The problem of dazzle*

When driving at night every motorist experiences difficulty from the dazzle of approaching headlights, especially if undimmed. Glare of this sort may be followed by a dangerous interval of defective dark adaptation before the eyes adequately recover vision. What is the best way to avoid this hiatus in visibility? Experienced night drivers will be found to adopt one of the following techniques:

(1) The commonest method is deliberately to keep from looking at the advancing headlights directly. The gaze is kept all the time on the near side of the road. This method is successful if the driver keeps his mind rigidly on his task.

(2) A second common method is to shut the left eye, opening it again after the glare has passed. It is an interesting fact that one eye may be dazzled independently without affecting the other. The efficacy of this method depends on how speedily the driver learns to suppress confusing after-images from the dazzled eye. Drivers say it takes a little time to learn the trick of suppression. They use this procedure particularly when the approaching light appears suddenly, as when the approaching car is coming unexpectedly round a bend in the road.

(3) An elaboration of the same technique is to keep the left eye open but to shade it. A commercial traveller attended a fancy dress party at which he wore a large and impressive false nose. On leaving the party he inadvertently still wore the nose, which he soon discovered was very useful for night driving. By a tilt of the head he could make the shadow of the false nose cover his left eye so that it was shielded from advancing headlights. Wearing a comic nose has its disadvantages if a driver is stopped at night by the police. He therefore later elaborated the idea by making a central vertical septum of blackened metal which he attached to the front of his distance glasses.

(4) *Dark glasses* can help against dazzle, but at the expense of lowering general visibility. This also applies to the gold-spattered anti-glare glasses formerly popular.

(5) *Polarization.*—It would be possible to eliminate dazzle to a large extent by polarizing light from headlights in one plane, while drivers wore glasses which polarized in a plane at right angles. The main trouble would be expense which at present rates would add about 33% to the cost of a headlamp. Another disadvantage is that the use of polarizing media in front of headlamps would greatly diminish the intensity of the light transmitted. To give adequate illumination of the road a much higher candle-power lamp would be necessary than that possessed by ordinary cars at the present time. This would increase the cost of motoring.

Perhaps this is the place to mention some other polarization phenomena. During the manufacture of laminated glass windscreens the layers of windscreen are made to undergo pressure. Inequalities of pressure may cause areas of windscreen subsequently to polarize transmitted light. Reflected light from a wet road is also partially polarized. Hence when travelling over a wet road at night with a dry windscreen it is often possible to note linear patterns on the windscreen where the polarization is contrary to the reflected road light. These lines are altered if moisture runs down the windscreen, because such moving fluid itself has a polarizing action. These phenomena materially affect visibility in driving.

The effect of dirt and dust on the windscreen and windows is worth study. Dust may produce diffraction effects such as small coloured haloes. Raindrops on windows or windscreen frequently produce distortion of the outside scene.

(6) *The deliberate use of dazzle.*—Most motorists have experienced unpleasant dazzle when the headlight of a car behind strikes the back window. The driving mirror is cut of action at once. A rear window blind is often fitted to cars for this reason, or alternatively a curved rear window glass which prevents the parallel rays of the following headlight from annoying by bringing them to an approximate focus. These devices prove only partially effective.

Police flying squads find dazzle from behind an effective weapon against car bandits. As they follow a fugitive car zig-zagging at top speed through side streets at night, the police try to follow close behind and concentrate their headlights upon the bandit car. They sound their gong, and the average car bandit in his excitement accelerates wildly. His faulty cornering and defective vision in the dazzle will cause him to crash unless he has displayed the foresight to steal a car with an efficient rear blind.

(*b*) *The Problems of Reflectors*

Properly adjusted reflectors on the backs of cars are a great help in making night driving safe. The ordinary reflectors depend on internally reflecting prisms and their "cube-corner-facets" reflect light efficiently if properly mounted. The regulations prescribe that such reflectors must be set at right angles to the baseline of the car both vertically and horizontally. These regulations are more honoured in the breach than the observance. Most car backs these days are curved posteriorly. If the reflectors are just screwed on flush with the posterior surface of the car, they are ineffective. Light from a following car is not reflected back to the driver of that car, but outwards and upwards. It is thus rendered useless.

Cat's eyes down the middle of the road are a great help to the night driver. Some roads have red reflectors down the near side and these have definitely proved their value. If these reflectors have colourless reflectors on their reverse side there is the advantage of a line of colourless reflections on the offside of the road too. This arrangement is being adopted by many authorities.

There is a good deal to be said for making cars carry colourless reflectors on their sides. This might be a help when cars reversed out of their front drives, or occasionally at cross roads.

The Times recently described a strip material known as "Scotchlight" which could be employed as a reflecting armband for pedestrians, or made into small portable reflecting danger-signs which could be stood in the road behind a car when the motorist was changing a tyre.

The hypermetropic eyes of animals, especially where the tapeta lucida are well developed, make excellent light reflectors at night, so that it is often possible to spot in this way a cat or dog in the road. The reflections from animal eyes can be seen from a much wider angle than the standard prismatic reflectors. A fortune awaits some manufacturer who will imitate animal eyes in the form of a glass lens inside a suitably curved reflecting base. Such ocelli could be in the form of buttons. One or two such button-ocelli sewn on the back of the overcoats worn by pedestrians would give a high degree of protection to the wearers.

It is quite remarkable what a high degree of protection is given even by such a simple object as a white scarf, which will greatly increase the visibility of its owner to the night-driving motorist.

Sometimes reflections from headlights may be of disadvantage to a motorist. If for instance there is mist or fog, the white light from the headlamp is reflected in diffuse fashion by the tiny fog particles. It is alleged that yellow headlights are not so liable to disperse reflection by the particles, and hence are better than white light.

In a foggy atmosphere there is commonly a clear layer of air below the fog on the surface of the ground. It is therefore advantageous for the foglight of a car to be down near the road surface, and also for the beam to diverge widely so as to illuminate the pavement edges before the car hits them.

(*c*) *Dark Adaptation and Night Driving*

Night driving brings up the following problems in which dark adaptation plays an important part:

(i) Motorists hate that uncomfortable period of twilight before lighting-up time. Shadows are falling, colour values are fading in accordance with the Purkinje phenomenon, and eyes have to peer to see an unilluminated cyclist or a pedestrian. There is still enough light from the Western sky to make headlights of minimal value.

It is at this stage that side and rear lights make such a difference. They act as indicators of the presence of vehicles, and also the careful driver can draw useful inferences. If, for example, the rear lights of the car in front swing out towards the crown of the road, the driver may well be overtaking a cyclist without lights, so precautions are taken accordingly.

The careful driver gives an oncoming car a little more clearance than its sidelights would suggest, because older makes of car often project laterally beyond the sidelight. Sidelights are meant as position indicators rather than as illumination to help the driver on his route. There would be a great deal to be said for making lighting-up times half an hour earlier.

Once headlights come into play other useful inferences may be made. If an approaching car suddenly accelerates the headlights lift suddenly because the weight of the car is flung on to its back wheels. If an approaching car seems to have its headlights constantly tilted upwards either the beams have not been properly adjusted to parallelism with the plane of the road, or alternatively the tyre pressures are down a bit and there is a heavy load on the back seat. If such a car brakes the beams will drop slightly.

(ii) A driver at a party may leave a brightly illuminated room and find himself very badly adapted to the surrounding darkness outside when the time comes to drive away. One has seen such a driver reverse his car in a car park straight into a car which seemed easily visible to a dark-adapted onlooker. A short time sitting in his car before starting would have allowed his eyes to become dark-adapted sufficiently to avoid the mishap.

(iii) A similar difficulty is often experienced when street lighting suddenly changes in intensity. Brightly illuminated streets are good in themselves, but they carry the penalty that a driver may suddenly run from a well-lit area into an island of comparative darkness. There is one such area just after passing the Houses of Parliament before reaching Millbank, where the bright lights are suddenly followed by inky blackness.

(iv) If one is unfortunate enough to get badly dazzled by a headlight, this problem of dark adaptation may become acute. It may even be necessary to give a slowing-down signal, run to the near side of the road, and stop.

(v) The driver with retinitis pigmentosa or similar pathological cause of night blindness does not seem a serious source of difficulty. Such a person usually finds it so difficult to drive at night that he is unlikely to be foolish enough to do so.

(d) Problems of Street Lighting

This is a fascinating subject for the illuminating engineer, who has to consider not only the intensity of illumination he desires but its cost. Monochromatic light from sodium or mercury vapour lamps is often chosen for its cheapness and efficiency in running. Such light is very irritating to many drivers owing to the gross distortion of the colour values of objects seen through its agency. Curiously enough other drivers allege that monochromatic light of this sort has a hypnotic effect. If they drive along a straight road illuminated by sodium vapour lamps they find themselves dropping off to sleep, conducive factors being the sense of unreality produced by the altered colour values, and the monotony of a long straight road stretching indefinitely ahead. Avoidance of this monotony can be achieved by planning the roads in gentle curves as found on many of the Continental Autobahnen.

Illuminating engineers aim to guide drivers by one of two methods. They aim for objects on roads to be seen by drivers either as darker silhouettes against a light background, or less usually as a light outline against the background of a dark road surface. The nature of the road surface thus affects visibility (Harris and Christie, 1951; Christie, 1954).

Away from well-illuminated roads, the beam of a headlight will give reasonable illumination where it impinges. Trouble arises from objects off the direct light of the beam, which may be visible only momentarily. The police lay very great stress in their handbooks on the degree of concentration and attention required for night driving. Harris and Christie (1954) have worked out that allowing for the number of vehicles on the road the chance of fatal accidents increases on average 1·88 times at night. They consider the reasons for this increased risk very largely visual.

(e) Visual Requirements for a Driving Licence

There is widespread doubt whether the simple recognition of the figures of a number plate at 25 yards as demanded for a driving licence is really adequate. A person may quite innocently state in his application for a driving licence that he can see such a number plate, and never realise that he has a constricted field from chronic glaucoma, or is night blind from retinitis pigmentosa. Ideally a motorist should have good visual acuity, a full peripheral field, good colour vision, good vision at night, and minimal heterophoria. Yet we all know drivers who have driven for years without accident with vision defective in one or other of these characters. It is difficult to steer a middle course between a "fuss pot" mentality and lazy *laissez faire*. The number of road casualties indeed has risen to horrifying proportions, but if every applicant for renewal of a driving licence required a visual test, who would undertake the enormous number of such tests necessary? There are certainly not enough ophthalmic surgeons or opticians.

My own solution would be the compromise one of including a better and more compre-

hensive visual examination in the driving test, and also compulsorily subjecting to a visual test all persons before the courts as the result of motor accidents, or for such motoring offences as dangerous driving, or driving without due care and attention. Disqualification should be automatic if reasonable visual acuity is absent and unattainable.

I wish to thank Dr. J. F. Fowler the physicist at King's College Hospital for his help with this paper, also Dr. W. May and Dr. P. Wright.

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Mr. H. C. Weston (Institute of Ophthalmology, London):

The visual problems of night driving arise entirely from the peculiar and often abruptly changing luminous field of view, which determines both the momentary visual capacities of the driver and the apparent content—and, hence, the intelligibility of the continuously changing scene.

Both absolutely and relatively, the luminance values in the night field of view differ much from those of the day field. From those parts of the field having sub-liminal brightness no useful information can be received: it is as if there were blind areas in the somatic visual field. In other parts, small patches of brightness are substituted for—and must be interpreted as representing—what, in daylight, are much larger areas of different brightness, colour and contour. In yet other parts, new brightnesses are added, some aiding and some hindering the rapid development of perceptions which we hope will be valid for the journey moment by moment.

The distribution of brightness in the night scene may not be merely such that the way ahead is so difficult to discern that the driver is compelled to proceed slowly and warily. It may be actually misleading so that, although confident he has solved the visual problem of the vista, on closer approach the solution is found to be incorrect and an emergency operation is required to avoid calamity.

Inclement weather generally increases the visual stress in driving both by day and night, but its adverse effect is always greatest at night. Then, it still further impoverishes a field of view already emptied by darkness of many features which ordinarily give rise to helpful visual impressions, including those parafoveal streams on which judgments of speed and distance largely depend. But, unlike darkness itself, it does not simply fail to reveal but intrudes new and disrupting features into the field and distorts the appearance of others. Rain is the most usual though not, of course, the worst of inclement weather for night driving. It gives a streaky appearance to lighted road surfaces, and against such a background objects in the dark areas are difficult to see. From the driver's viewpoint the situation is still worse, because his rain-spotted or streaming screen is superimposed on the external scene, so that parts of this, particularly the lateral and foreground parts, are made more indistinct. One of the major problems confronting the street lighting and highway engineers is to devise a system of lighting and a road surface that, while meeting other important requirements, will yield a satisfactory road appearance in wet as well as in dry weather.

Driving a motored vehicle at any time calls for ceaseless vigilance. Yet, except for road transport drivers on night shift, driving at night is usually done by people who are already fatigued by their daytime activities. Fatigue is insidious in onset and momentary failures of attention, as well as misperceptions, are among its earliest manifestations. They occur before there is any awareness of fatigue, yet, at night, unflagging attention and perceptual agility are especially necessary in view of the relatively unfavourable presentation of the changing scene.

Unlike Argus who could see all with his hundred eyes, we have only two and their gaze has to be directed to and almost continuously kept within a portion of the scene ahead which has small angular dimensions. Except on traffic congested roads, attention has to be given to the road some hundreds of feet ahead of the vehicle, this sighting distance being varied, of course, according to the speed of driving. A common sighting distance at moderate speeds in built-up areas is one of about 300 feet and, at this distance, the whole width of the road, most of the objects of interest to the driver and most of the visible light sources occupy quite a small portion of the total visual field (Fig. 1). It may be easy to visualize how small this driver's fixation field is if I say that it can be covered by a couple of postage stamps viewed at the conventional reading distance of 33 cm.: its angular subtense is about 8 by 5 degrees. Two points should be noted: (*a*) there is less tendency by night than by day to relieve the ocular muscles of static fatigue by occasional quick glances beyond the lateral

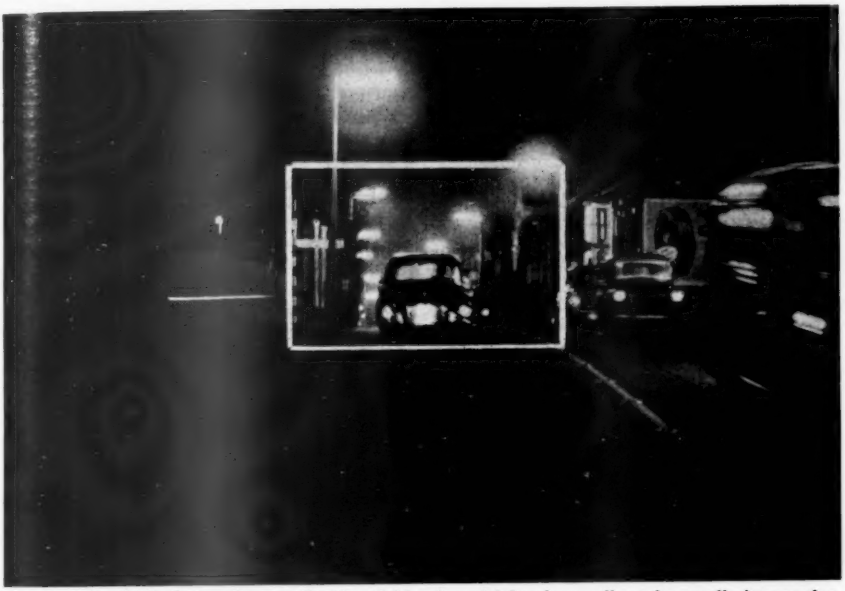


FIG. 1.—The field of attention, or fixation field, when driving is usually quite small: its angular subtense at the eye does not exceed about 8 × 5 degrees.

boundaries of this field—partly because it is more dangerous to do so, since the amount of information gained about what lies ahead is usually less than in daylight and is insufficient to give confidence that the fixity of the gaze may be relaxed even momentarily: (*b*) most of the street lamps—which are thousands of times brighter than any of the objects it is necessary to see—are crowded into this small field and so are imaged near the fovea where their glare effect is greatest. So far as the feeling of strain engendered by night-driving is referred to the region of the eyes it is almost certainly due to prolonged restriction of eye movements, in short, to staring—and partly due to restriction of blinking which always occurs during critical visual tasks. The more difficult the situation, e.g. when there is fog, the more sustained is the staring and the more acute the sense of strain.

Seeing while driving is obviously a paced task, like looking for faulty pieces among a stream of manufactured articles passing on a belt conveyor before an inspector. If the pace is too rapid and there are too many things in the display that should be observed before they pass out of sight, the perceptual load is too great, speed stress develops, and some of the objects which ought to be seen are inevitably overlooked. In the factory situation such oversights may not have disastrous consequences but they often have on the roads: accident rates are always higher in hours of natural darkness than in daylight hours, even on roads having good modern artificial lighting.

The artificial lighting of traffic routes is based on two principles. The first is to make the road surface, as seen in perspective by vehicle drivers, sufficiently bright for objects on the road ahead to be seen in silhouette, and the second is to do this without putting so much light from the street lamps into the eyes of drivers as to cause distraction, discomfort or any visual disability. To achieve a reasonably uniform and sufficiently high road brightness the lanterns must give an appropriate light output which they are designed to distribute in a particular way, such that the maximum beam intensity is at a fairly high angle from the downward vertical. The lanterns must also be mounted fairly high—25 feet is now general practice—and they must be appropriately spaced, usually from 100 to 150 feet apart. From the driver's point of view each lantern produces on a dry road surface a patch of relatively high brightness of T-shape, the patches from successive lanterns merging together so that the whole road ahead is fairly evenly brightened. Under these conditions, the visual problems of night driving are not very troublesome on uncongested roads, but this scheme of things is upset when the road is wet.

There are different types of lighting in use on traffic routes. For example, the lanterns are sometimes centrally suspended but more frequently they are staggered on either side.

If they are of what is called the cut-off type they need to be more closely spaced to obtain sufficient uniformity of road brightness but they have the advantage of giving less glare.

As to the kind of illuminant, six kinds are now in use—gas, incandescent tungsten, mercury discharge, colour-corrected mercury, sodium and fluorescent. It is impossible to compare these fairly on the road since they are used in installations which differ in other respects. But there is some evidence, that, given comparable installations, the monochromatic sodium light has some advantage as a driving light, and fluorescent light is also good.

If street lamps are so widely spaced—as they are in side roads—that there are extensive dark areas in the road, the detection of pedestrians and other unlighted objects which are in very poor contrast with such backgrounds requires the most intent looking and may be quite impossible. In side roads generally, and especially if one is unfamiliar with them, driving with car side-lamps alone not only makes the visual task of the driver often extremely difficult and trying, but can also be dangerous. Car side-lamps are intended to indicate the presence of the vehicle to other road users and not to provide a driving light. Unfortunately, pedestrians do not always realize that they can see a car by its side-lamps before the driver can see them.

Nothing is gained by using headlamps on stretches of main roads provided with the most up-to-date street lighting but, just because these stretches are so well lighted, in passing out of them to unlighted or dimly lighted roads dark-adaptation cannot occur quickly enough to ensure safe vision until an appreciable distance has been travelled. One way of overcoming the difficulty would be to scale down the street lighting gradually instead of changing or stopping it abruptly, but this is not likely to be done very generally. As things are now, dipped headlamps need to be switched on *before* leaving a well-lighted road. On unlighted roads when vehicles provide their own flarepath, objects on the road ahead are revealed by being made brighter than the surface which forms their background—the silhouette effect is reversed.

The headlights of oncoming vehicles make the road surface ahead of them appear brighter to an approaching driver than the surface illuminated by his own lamps and so objects in this part of the road are seen as they are in lighted streets. The lights of oncoming vehicles are sometimes very helpful in this way to a driver travelling in the opposite direction, as they may also be in revealing bends in the road. But the bugbear of night driving on unlighted roads is the frequent momentary exposure to the glare of undipped approaching



FIG. 2.—On this wet road the zebra crossing is almost invisible although it is floodlighted, but the flashing beacons indicate its presence.

headlamps and, unfortunately, to the more prolonged glare from maladjusted lamps even when they are dipped. To resist the phototropic effect of these bright light sources requires an effort of which we are often very conscious. At best, driving on unlighted roads nowadays involves frequent dipping of lights and consequent sudden shortening of seeing distances. Speed ought to be and often has to be reduced when these abrupt changes in visibility occur, but there are numerous occasions when during deceleration a considerable distance is travelled almost blindly. For a short period progression is more of an act of faith than a visually guided one, and this is also sometimes true when passing vehicles moving in the opposite direction on fairly narrow roads. A new problem of glare seems to be developing, due to the practice of equipping new cars with bigger and brighter stop and tail lamps. Stop lamps have to be bright enough to be unmistakably visible in daylight and this means that they may be unnecessarily and glaringly bright on dark roads by night. Something may have to be done in the future to make the brightness of such lamps adjustable for day and night driving.

Driving on empty unlighted roads provides most of the visual conditions favourable for the onset of the hypnotic state: an almost empty and monotonous visual field save for the relatively bright ribbon of road ahead to which the gaze is glued. There is something to be said then for having other vehicles on the road: their lights contribute to the visual stress of night driving but, at least, they help to keep the driver awake!

The visual problems of night driving have been added to in recent years by such innovations as roundabouts and zebra crossings. Signs giving advance warning of roundabouts are not always easy to see, nor are some other road signs. Roundabouts which are unlighted and not otherwise noticeably marked—as by a black and white curb or fence may not be seen in time to be negotiated when driving a car fairly fast on a gently curving or undulating road which is traffic free and apparently safe for fast travel. Accidents have shown the need for making roundabouts clearly visible and many are now suitably lighted or marked. Zebra crossings would often be difficult or impossible to see at night but for their beacons. As seen by the approaching driver, their distinctive white stripes are much foreshortened and the contrast between the white and black stripes may be insufficient to make the crossing conspicuous. When the road is wet, the contrast between the stripes may vanish completely—even if the crossing is floodlighted. Hence the beacons are very necessary indicators of the presence of a crossing (Fig. 2). Since, if steady, their lights could be overlooked, or their significance not realized—especially in localities where there are numerous other lights in the parafoveal field of view—it was a wise decision to make them conspicuous by flashing.

Mr. G. Grime (Road Research Laboratory, Department of Scientific and Industrial Research, Harmondsworth, Middlesex):

Road Illumination by Headlamps or Street Lamps

Consideration will be confined in this paper to problems of seeing with headlights and in street lighting.

The Importance of Improving Seeing at Night

An analysis of the figures for adult pedestrian casualties at night was made by Smeed (1953), in which he considered the changes in casualties which occurred when summertime was introduced and removed. In the hours that change from light to dark he found that casualties were approximately doubled, while in those that change from dark to light, casualties were halved. There is therefore scope for very considerable accident reduction by means of improved lighting.

Table I illustrates the relative importance of town and country as regards accidents. About twice as many serious and fatal night accidents occur in built-up as in non-built-up areas. This emphasizes the importance of making improvements in street lighting.

TABLE I.—ACCIDENTS IN DAYLIGHT AND DARKNESS, GREAT BRITAIN, 1954

Light conditions	Number of fatal and serious accidents: Built-up areas	Non-built-up areas
Daylight	25,500	12,200
Darkness	11,000	6,300

For street lighting there is reliable evidence of the improvement likely to result from re-lighting to modern standards. Tanner and Christie (1955) found that after re-lighting eight London streets to the upper limit of Group A lighting, there was an average reduction of 35% in personal-injury accidents.

Unfortunately, similar figures are not available for improvements in vehicle lighting.

The Physics of the Road Illumination Problem

For ease in driving at night, the lighting system, whether provided by street lighting or

by headlamps, must do two things: (1) enable objects on the road to be detected in good time, and (2) enable the driver to position his vehicle accurately in relation to the kerb and to other vehicles. The importance of the second requirement has not always been sufficiently realized when designing either vehicle or street lighting systems.

In satisfying these requirements, the lighting engineer is subject, for economic reasons, to a severe limitation in the amount of light which he has at his disposal. Brightness levels are therefore always extremely low compared with daylight; colour sensitivity is largely lost and so is the ability to resolve small details. The visibility of objects then depends mainly on the existence of a brightness contrast between the object as a whole and its background. Silhouette vision occurs when the object is the darker, and reversed silhouette vision when the object is the brighter. In seeing with vehicle headlights, the reversed silhouette is the more important; the object is illuminated by the headlamps and appears bright against a background of dark road surface. Objects are also seen, but less reliably, as dark silhouettes against road illuminated by the oncoming vehicle's headlights. In street lighting, where the object of the lighting engineer is to make the road surface as bright as possible, the dark silhouette is by far the more important (Fig. 1).



FIG. 1.—In lighted streets vision is mainly by silhouette. Occasionally the silhouette is reversed in the case of a pedestrian wearing light-coloured clothing.

Vehicle Lighting

In designing and using vehicle headlights the most difficult problem is to provide good seeing with minimum glare, when meeting another vehicle. The lamp designer's difficulties in attempting to solve this problem arise mainly from the smallness of the angular separation between the object, which needs the maximum illumination, and the oncoming driver's eye, at which, to avoid dazzle, illumination must be a minimum. Fig. 2 shows that, for a high visibility distance and a tolerable amount of glare at 400 feet, the intensity must drop rapidly between two points separated by only about 3 degrees. These remarks, of course, apply only to the "meeting beam" or dipped beam, used when another vehicle is approaching. The driving beam used on the open road presents no particular problem.

Lighting has to satisfy the two requirements of object detection and position keeping. Experimental techniques are now available for testing how well both requirements are met. The first gives a straightforward measurement of the distance at which a driver can recognize an object on the road in front of his vehicle when faced by another vehicle. Two test cars

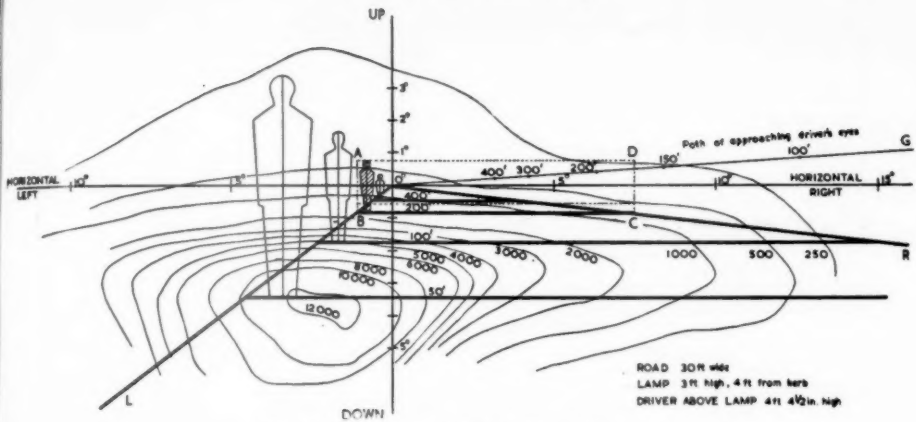


FIG. 2.—Geometry of headlighting problem.

are equipped with similar headlamps, properly aimed, and with apparatus for measuring distance. They start simultaneously from opposite ends of a test track, usually straight and level, along which objects of a dark colour are placed at intervals. The distances at which the driver sees the test objects are recorded by means of apparatus carried in the car. At the Road Research Laboratory a simplified form of this test has been used, in which one car remains stationary to provide the glare source, and the other carries the observer. Only one test object is used, placed near to the glare source but on the opposite side of the road. A further simplification was to employ beams of uniform intensity.

The results of many trials of this kind have been combined to produce the curves of Fig. 3 which enable the performance of a meeting beam to be determined when its light

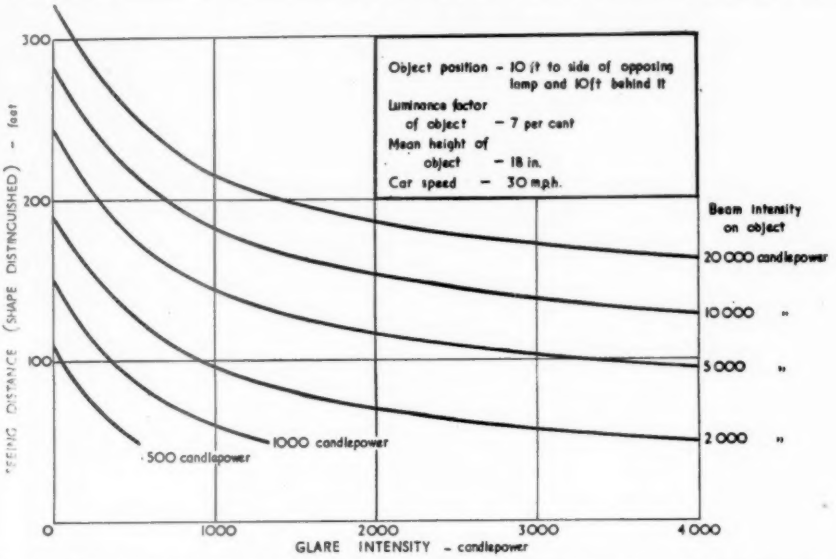


FIG. 3.—The relation between seeing distance, beam intensity directed at an object, and glare intensity.

output in different directions is known. Fig. 3 gives only a single figure for the minimum visibility distance in a particular meeting situation, but the calculations can readily be extended to cover other situations by making use of well-established physical laws relating the effects of glare to the angle between the glare source and the eye of the observer.

Tests of visibility distance alone are not sufficient to determine whether a meeting beam is satisfactory. A narrow pencil beam, for instance, may give a high visibility distance and yet be extremely unpleasant to drive behind because it throws little or no light on the road near the car. A test has therefore been developed which gives an indication of general performance and of the comfort of driving with a particular beam. The usual way of carrying out tests of this kind is to use the lamp in the ordinary course of driving on the public roads. A serious objection to this as a method of test is that it is not fair to judge a lamp by its performance when meeting anything but a similar lamp, and that this is not possible on the road. The objection can be overcome by making the assessment on a test track in such a way as to approximate to road conditions. The experiments (Grime, 1954) were made on a straight track about half a mile long, having man-size obstacles in two rows, one on each side of the track, and a line of smaller obstacles in the middle. The obstacles were an important feature of the procedure, since they compelled the drivers to concentrate on the task of driving. It was intended in this way to remove some of the artificiality of the tests. Two cars took part in the test, starting simultaneously from opposite ends of the track; each car carried the two sets of meeting beams to be compared. Eight runs were made using alternately one beam or the other, and the drivers then completed a questionnaire recording their preference. Runs were also made with the road surface wet. In most of the experiments, all the driver had to do was to make a direct comparison, and this helped greatly to increase the consistency of the results.

The main conclusions of these and other researches were:

(1) When the lamps are new and properly aimed most modern meeting beams provide similar visibility distances. Only small improvements in visibility distance are likely to result from further design changes.

(2) On British roads, however, headlamps are rarely aimed correctly, and many have deterioriated so that they emit no more than a feeble gleam of light. Many drivers are dazzled, and many are able to see only a very short distance. The aiming of lamps is so poor and the deterioration of lamps is so marked, that the most effective single step to increase visibility and reduce dazzle would be to bring up all headlamps to a similar state of efficiency and correct aim.

(3) Dazzle is determined not by the opposing glare intensity alone; it is decreased by the foreground illumination from the driver's own lamps. Thus, dazzle depends on one's own lights as well as on those of the oncoming car, and the driver of a car with feeble lights will be dazzled even by headlights in good condition and properly aimed.

(4) Broad beams, even of low intensity, are preferred to narrow ones, giving the driver greater confidence. The correctness of the design of the modern headlamp, in which a large proportion of light is spread widely over the road near the car, was confirmed.

An account of most of this work has been given by Harris (1954).

Street Lighting

The lighting engineer's problem in street lighting is to provide a well-illuminated background, usually the road, against which objects are seen in silhouette.

Each single street-lighting lantern produces one patch of light on the road. The art of street lighting is to combine these patches into a pattern of light on the road which satisfies the two requirements of object detection and position keeping. It was formerly thought that these objects could only be achieved by making the carriageway uniformly bright; we are now beginning to change our minds about this, and to think that certain kinds of non-uniformity are permissible. For example, a pattern of horizontal bands of light might reveal pedestrians and vehicles perfectly adequately and would therefore be acceptable, although it might not enable small animals to be seen at a distance.

The diverse types of street lighting are more fundamentally distinguished by differences in the distribution of light from the lanterns, than by more obvious differences such as colour of light and shape of unit. The two most dissimilar distributions are termed "cut-off" and "non-cut-off".

"*Non-cut-off*" *lighting.*—In this system most of the light is emitted almost horizontally up and down the road, and the patch of light from a single non-cut-off lantern is T-shaped, the tail of the T extending along the road towards the observer. The light is reflected from the road surface at small angles, generally less than 5 degrees. The whole pattern is obtained by combining the patches from individual lamps, and the result is a pattern of longitudinal patches.

The advantage of the non-cut-off system is its cheapness, since the lamp-posts may be widely spaced.

The disadvantages are, first, the high glare, especially when the road surface is a dark one and secondly, that it may become very poor and streaky when the road is wet, the long brilliant streaks producing particularly confusing patterns in these circumstances.

Cut-off installations.—As the name suggests, in cut-off lighting the tail of the patch is cut off and light is not allowed to be emitted near the horizontal. The individual patches run transversely across the road and there is very little glare.

The disadvantage is that a closer spacing of lamps is required than with non-cut-off lighting, and the installation is therefore more costly.

Intermediate systems.—Most modern British street lighting installations are compromises between the two extremes of cut-off and non-cut-off (Fig. 4).



FIG. 4.—Transitional lanterns intermediate between high- and medium-angle beam types.

The Road Surface

All these systems of street lighting have as their object to make the road surface bright as a background against which objects may be seen. The properties of the road surface are therefore of great importance in street lighting, and a substantial part of our work at the Road Research Laboratory on street lighting has been concerned with the study of the road surface as a reflector of light striking it at various angles (Christie, 1954). It is found that road surfaces act as "preferential diffusers", reflecting strongly, almost as in a mirror, at the tail of the light patch, but only very weakly and diffusely at the head of the patch near the lantern. The dominant factor in determining the reflection characteristics is the texture of the road surface, smooth surfaces producing long bright patches and rough ones shorter and less bright ones. Texture is particularly important in wet conditions, when a certain coarseness of texture is necessary in order to avoid the formation of a streaky and confusing pattern.

It has been shown, both theoretically (Christie, 1954) and practically, how important the road surface is in street lighting, and indeed it may be calculated that making the road surface lighter by a factor n has a greater effect on visibility than increasing the light output of the lanterns in the same ratio.

The road surface is perhaps of less importance in conditions where headlamps provide the lighting than in street lighting, but probably has a considerable influence on driving comfort. There is no general agreement, however, as to the relative merits of dark and

light road surfaces. Dark backgrounds should, in theory, enable objects on the road to be detected at greater distances than light ones; but from the few tests which have been made, the increase does not appear to be great. At the same time, there is indirect evidence that light-coloured diffusing surfaces are better than dark from the point of view of general comfort in driving, good position keeping, and reduction of dazzle. The evidence was obtained in the tests of general performance and comfort, where it was found that a broad beam, lighting up the road near the car, helped position keeping, and that a bright foreground reduced dazzle; a light-coloured road surface helps to produce a brighter foreground and to extend the width of the patch of light on the ground, and may therefore be expected to have the same effect as broadening the beam and increasing its intensity. More research is, however, required to define the optimum properties of the road surface.

This paper is presented by permission of the Director of Road Research.

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Mr. Grime, in reply to the discussion, said that he would not like the question of polarized light to be dismissed as academic only. It was, of course, one of the very few solutions which offered an improvement in the ratio of the useful light to the glaring light put out to the other driver. It was true that with present windscreens there was a "chicken-wire" pattern due to the rotation of the plane of polarization through the windscreen and that had to be improved, or the other type of screen, the laminated type, which was very nearly as good as plain glass, must be used. The Road Research Laboratory had carried out quite a number of experiments on this and the main difficulties were still the psychological ones and the question of comfort in driving. When meeting another car one could undoubtedly see nearly twice as far with polarized lighting systems as with other types, but one had to look through a vizor which cut off half the light coming from the field of view and it was most unpleasant, since one wanted to look round it. It was possible to wear half-glasses in which the one half was polarized but that meant that one had to use two different positions for the head in driving, and one had to dip the head quite an appreciable amount because with the normal type of spectacle the lens was very close to the eye and the pupil subtended quite a large angle. Experiments were being made at the moment with mixed systems in which more light was put in the foreground than one could get with a polarized system in which a reasonable amount of power was used and it looked as though that kind of system might render a limited solution possible.

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Section of Odontology

President—J. A. S. WRIGHT, A.F.C., F.D.S. R.C.S.Eng., H.D.D., F.D.S. R.C.S.Ed.

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Basic Aspects of Mouth Development

By C. H. TONGE, T.D., M.B., B.S., B.D.S.

Reader in Oral Anatomy, University of Durham, King's College, Newcastle upon Tyne

THE mouth develops in unison with the other organs and tissues and cannot be considered without reference to the embryo as a whole. In embryonic and fœtal life, the visceral part of the head, including the facial structures and portions of the alimentary and respiratory systems, has a much slower rate of growth and differentiation than the neurocranial part. The primitive oral cavity or stomatodæum forms a portion of both the nasal and mouth cavities, the remainder arising from an inclusion of the primitive pharynx following the breakdown of the buccopharyngeal membrane. During the formation of the boundaries of the oral cavity, fusions occur which involve the fronto-nasal process, as well as the maxillary and mandibular processes of both sides. Failure of growth and union of these components in an orderly and mainly symmetrical manner results in malformations which may involve the face and the oral and nasal cavities in varying degree.

The aim of this study of mouth development is to consider the various phases of differentiation, with particular reference to their characteristic features and functional significance.

MATERIAL AND METHODS

Serial microscopic sections, cut sagittally, coronally and transversely, of 23 human embryos and 16 fœtuses were examined, together with representative wax plate reconstructions. Streeter (1942–1951) conceived the idea of dividing embryonic life into a series of horizons, demarcated as stages in development, then allotting each of the normal specimens of the Carnegie Institute Collection to its appropriate phase. The material used in this study has been graded in Streeter horizons and the ovulation age of each of the horizons indicated. In addition, the crown-rump measurement of each specimen is stated, and, where appropriate, reference is made to embryos described in the literature. The material examined ranges from the fourth week to the fifth month of intra-uterine life.

OBSERVATIONS

The 7-somite embryo of about 22 days' ovulation age, described by Payne (1925), emphasizes the development of the neurocranial part of the head and shows the presence of a large head fold. The stomatodæum is bounded by the developing fore-brain area above and the pericardial area below. The mandibular arches are at the sides and reach towards the pericardial area, whilst the processes which give origin to the lower jaw are not yet demonstrable. It is open ventrally, and dorsally the buccopharyngeal membrane with its ectodermal and endodermal layers separates the stomatodæum from the region which later forms the fore-gut.

The mandibular and hyoid arches are seen as surface elevations in embryos of 13–20 somites (horizon XI, ovulation age 23–25 days). They are also present in the 13–14-somite embryo described by Low (1908). The buccopharyngeal membrane is shown to be perforated in illustrations of a 20-somite embryo (Davis, 1923) establishing a free communication between the stomatodæum and the primitive fore-gut. The first three branchial arches are present in embryos of 21–29-somites (horizon XII, ovulation age 25–27 days), and partial fusion of the mandibular processes as they grow forwards may be observed in the older specimens of the group.

In a 5 mm. specimen (horizon XIII, ovulation age 27–29 days), the mandibular processes are meeting and fusing in the mid-line to form the floor of the stomatodæum, whilst the pericardial bar is gradually descending. In sections cut in the transverse plane, the embryo is seen to be lying completely within its amniotic sac; the fronto-nasal process, mandibular and hyoid visceral arches, as well as the dorsal surface of the embryo can be identified. The mandibular processes are separated ventrally and the first aortic arch artery can be seen traversing the mandibular arch tissue (Fig. 1).

In specimens of 5·6 mm. and 7 mm. (horizon XIV, ovulation age 28–30 days) the mandibular and hyoid arches are large and form prominent surface features. The maxillary process appears and the line of junction between the mandibular and maxillary processes forms a lateral wall for the mouth cavity defining the cheek. The fusion of the mandibular processes proceeds to completion forming the area of the lower jaw and the greater part of the floor of the mouth. The pattern of the tongue takes shape receiving elements from each of the first three visceral arches. The growth of the mandibular arches to form the lingual swellings creates a deep intermandibular sulcus in the mid-line region. The upper jaw and roof of the mouth is less well formed than the lower jaw and floor of the mouth. The maxillary processes are widely separated and the common bucco-nasal cavity is a cleftlike structure with a central diverticulum, Rathke's pouch arising from it (Fig. 2).

During the formation of the walls of the oral cavity, fusion of processes takes place. Union of the mandibular processes continues into later phases of development. The complete separation of the buccal and nasal cavities occurs last, by the union of the two palatal shelves of the maxillary processes with one another, and with the lower edge of the nasal septum. In Fig. 3 the mid-line fusion between the mandibular arches is seen. The surface epithelium consists of a single layer of flattened cells with well-marked heavily-staining nuclei. This clear-cut definition fades sharply in the region of contact of the two epithelial layers. The cells in the line of fusion are enlarged, pale and opaque near to the surface, whilst in the deeper areas, the definition between the adjacent cells is no longer clear, and many show abnormal and abortive mitosis. These phenomena suggest that the process of degeneration is slow. The mesenchymal cells are orientated with their long axes parallel to the epithelial cells in the line of fusion. As the epithelial cells disintegrate the mesenchymal cells re-orientate and bridge the gap, thus forming a continuous mass of tissue.

The formation of a face and the establishment of an upper jaw and primitive palate from the premaxillary process, as well as a primitive nasal cavity and bucco-nasal membranes between the nasal and oral cavities, characterize the four specimens, two 11 mm. and two 12 mm., allocated to horizons XV–XVII (ovulation age 31–36 days). During these phases continued growth occurs in the lower jaw and the mandibular division of the trigeminal nerve is larger than the maxillary division.

A 15 mm. specimen cut transversely, and two 15 mm. and a 16 mm. cut sagittally were placed in horizon XVIII (ovulation age 36–38 days). During this stage the nose and upper jaw are clearly discernible on the surface, the bucco-nasal membranes break down resulting in the formation of the primitive posterior choanæ. It is, also, the stage in which individual structures and the pattern of the musculature can be identified in the lower jaw region. Bartelmez and Evans (1926) showed that the cranial nerve complexes preceded mesenchymal tissue condensations in branchial arch fields. Fawcett (1905) showed that the mandibular nerve was the first structure to become differentiated in the lower jaw of man. Bardeen and Lewis (1901) as well as many others have identified pre-muscle condensations by tracing the main nerve supply to a region and following branches to them. In defining the individual muscle groups in the region of the mouth, similar techniques have been employed in this series. The lingual and inferior dental nerves can be seen, the former medial, the latter lateral, to the condensation which is the pre-cartilage phase of Meckel's cartilage. The nerve and artery to the mylohyoid can be traced and the mylohyoid and anterior belly of the digastric muscles demonstrated. It was not possible, however, to ascertain whether the mylohyoid and anterior belly of the digastric were formed from two separate condensations or arose from the same condensation. A wax reconstruction of one of the specimens examined at this stage and cut in the sagittal plane shows that the external surface of the face is established and the primary fusion lines completed. The floor of the mouth is formed and a primitive cheek mass identifiable. The primitive palate or premaxilla represented the only part of the true roof plate of the mouth. An early stage in the formation of the secondary palate could be seen as an inward growth of the palatal shelf of the maxillary processes. The site of Rathke's pouch was still visible. The tongue is well formed, its anterior two-thirds being more than ten times larger than the posterior one-third. The sulcus between the two parts of the tongue is clearly marked. Similarly, the vallecular fossa and epiglottis can be observed. The vestibule of the mouth has not yet formed since lip separation has not commenced. Microscopic examination of these specimens indicates that a considerable differentiation of the structures within the area of the floor of the mouth has taken place. The lingual nerve and submandibular ganglion, the mental, incisive and mylohyoid branches of the inferior dental nerve, as well as the hypoglossal and vagus nerves can be identified. Meckel's cartilage with its sheath and the cartilage of the second arch can be seen in their pre-cartilage stage. The condensations for the mylohyoid and anterior belly of the digastric muscles with the nerve to the mylohyoid between them are identifiable. Another zone of condensing mesenchyme marks the area in which the mandible will later ossify. The submandibular salivary gland has not commenced its differentiation

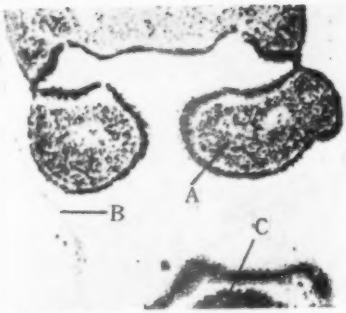


FIG. 1.—Transverse section of a 5 mm. human embryo. A, Mandibular process; B, Amnion; C, Fronto-nasal process. ×79.

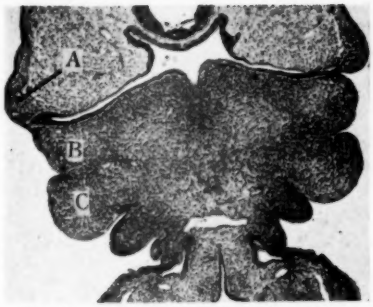


FIG. 2.—Transverse section of a 5·6 mm. human embryo. A, Maxillary process; B, Mandibular process; C, Hyoid arch. ×30.

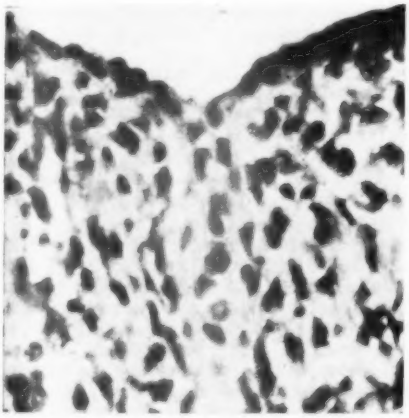


FIG. 3.—Mid-line area between the mandibular arches in a 5·6 mm. human embryo. ×600.

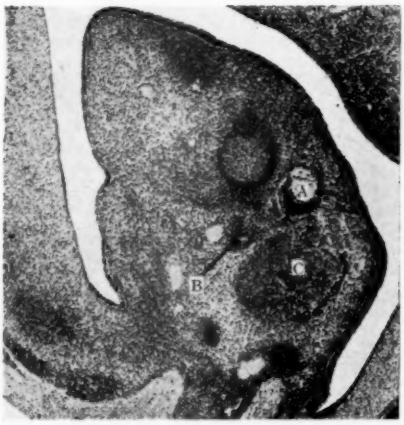


FIG. 4.—Sagittal section of a 16 mm. human embryo. A, Lingual nerve and submandibular ganglion; B, Mylohyoid muscle; C, Submandibular gland mesenchymal condensation. ×43.

but the mesenchymal bed into which it grows can be seen (Fig. 4). The muscles of the floor of the mouth and tongue are made up of condensed areas of cells in which it is not possible to label myoblasts as distinct from fibroblasts. There is, however, some general tendency for elongation of the cells in one direction and some cells are already more elongated than others.

Four specimens, 18 mm., 18·5 mm., and two 19 mm. (horizon XIX, ovulation age 38–40 days), showed commencing osteoid deposition in the mandibular condensation and epithelial downgrowths for the parotid, sublingual and submandibular salivary glands.

Specimens of 20 mm. and 20·5 mm. (horizon XX, ovulation age 40–42 days) indicate that the maxillary process is becoming larger in size and depth. The palatal shelves of the maxillary processes are actively growing towards one another. The placodal area has grown inwards and the olfactory mucosa can be seen near to the roof of the nasal cavities. The nasal septum is growing downwards and a mesenchymal condensation is seen in it, preparatory to the formation of cartilage. The vomero-nasal organs are identifiable as invaginations from the surface of the nasal epithelium. The mouth cavity has breadth but negligible height, the area of the cheek is limited and the separation of the lip to give rise to the vestibular sulcus is just commencing. The parotid outgrowth is formed of a solid mass of epithelial cells which will later canalize and from which the parotid outgrowth lying upon the tissues of the first visceral arch is an early recognized structure of the cheek. The tongue still occupies a large part of the common bucco-nasal cavity and its musculature shows its

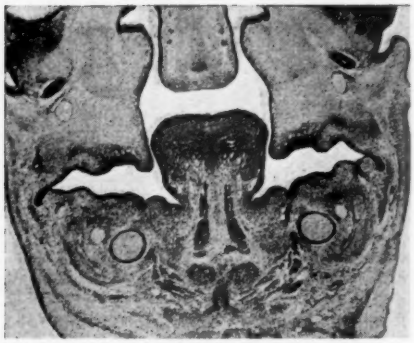


FIG. 5.—Coronal section of a 20·5 mm. human embryo. The common bucco-nasal cavity and the palatal shelves of the maxillary processes are seen. ×17.

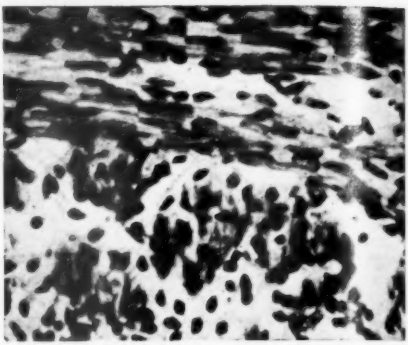


FIG. 6.—Sagittal section of a 28 mm. human embryo. The geniohyoid muscle is cut longitudinally and the mylohyoid transversely. ×517.



FIG. 7.—Coronal section of a 31·4 mm. human embryo passing through the buccal and nasal cavities and showing mid-line fusion of the palatal shelves of the maxillary processes. ×16.

component units. The framework of the oral floor is strengthened by Meckel's cartilages, the mandible has started to ossify on its lateral side and the inferior dental nerve is lying in a gutter formed by the bone (Fig. 5). The myoblast cells in the developing muscles can be recognized—elongating cells with as yet single nuclei.

Specimens of 24 mm., two 25 mm., 28 mm., 28·5 and 31·4 mm. (horizons XXI–XXIII, ovulation age 42–48 days), show a gradual differentiation of the muscle masses and the platysma can be seen sweeping over the superficial tissues of the neck and chest wall. In Fig. 6, the geniohyoid muscle is cut longitudinally and the mylohyoid transversely in the 28 mm. embryo cut in the sagittal plane. The muscle fibres of the geniohyoid are multinucleated. The long axis of the fibre is in the direct line from the muscle origin to its insertion. It would appear that this arrangement has resulted from the rapid growth in length of the myoblast accompanied by the rapid multiplication of the nuclei as a result of nuclear division by mitosis or amitotis without a similar division of the protoplasm. The transversely cut mylohyoid shows groups of muscle fibres with interspersed fibroblasts forming the connective tissue of the muscle. The 31·4 mm. embryo which was cut in the coronal plane shows the fusion of the palatal shelves of the maxillary processes taking place in the mid-line. The nasal septum has not yet reached the level of the fusing palatal shelves. Ossification is proceeding in both mandible and maxilla. The more anterior fibres of the mylohyoid are below the level of Meckel's cartilage supported on their submandibular surface by the digastric muscles. The posterior part of the mylohyoid passes progressively vertically from above Meckel's cartilage towards the mid-line raphe (Fig. 7).

The pattern of formation of the boundaries of the oral cavity is complete with the fusion of the maxillary processes and the completion of the secondary palate. The next process traced in fœtal specimens is one of ossification, thus completing the formation of a hard and soft palate. As muscle differentiation proceeds myofibrillæ become formed. These are situated peripherally and are clearly visible in specimens of 80 days' ovulation age, although striations are not present. In specimens of approximately 117 days, muscle fibres with well-marked cross striations could be observed in the tongue musculature and that of the floor of the mouth.

Discussion

An examination of the sequence of events occurring in the development of the mouth results in the conclusion that normal growth depends upon the right environment being available at the right time. Any factor, genetic, hormonal, nutritional, general or local, which disturbs the time environment balance will produce abnormal growth. The degree and site of malformation depends upon the stage of embryonic development reached prior to the application of the factor causing the imbalance. The formation of the branchial arches, their vascularization, the fusion of processes involved in facial development, the innervation of the mandibular and maxillary processes, the appearance of independent mesenchymal condensations, the differentiation of visceral arch cartilages, muscle masses and bone all take place as a closely integrated pattern. The first essential must be an adequate nutrition to maintain growth. When the embryo consists of a small number of cells, its nutritional demands are low and there is no necessity for a circulatory system. As growth proceeds, a circulatory mechanism becomes essential and the early endothelial heart tube and blood vessels develop. The first aortic arch artery passing through the mandibular arch tissue, present from an early somite stage, is seen in the 5 mm. embryo (Fig. 1). It is the first recognizable independent structure within the mandibular arch. The progressive development of these embryonic tissues must depend upon an adequate nutrition, which in turn requires an increasingly complex vascular pattern and circulatory mechanism to be present. The cinematographic studies of Patten and Kramer (1933) in a nine-somite embryo indicate that cardiac contraction commences as irregular fibrillations in the bulbo-ventricular area. The vessel itself is probably formed as a differentiation from mesenchyme prior to the establishment of a circulation. Its further development is associated with changes in the endothelium. These may occur as a result of the force of cardiac pulsations (Stockard, (1915*a*, *b*)). The position of the vessel within the embryo and the influence of neighbouring structures may also be causal factors (Hughes, 1943).

The material examined suggests that the fusion of the mandibular processes is mainly occurring between 27–29, plus or minus 1, days' ovulation age. The fusions of processes forming the face and the primitive palate development from the premaxilla occur during ovulation ages 31–36 days. The fusion of the palatal shelves of the maxillary processes observed to be taking place in specimens of ovulation age 46–52 days is probably completed by the end of the second month. For normal development, it is necessary for these fusion processes to occur at a definitive time in embryonic life. If the time of fusion is in any manner delayed, then non-union remains permanent and continued growth of the separated processes causes them to become even more widely separated. In this connexion the work of Woollam and Millen (1956) is of considerable interest. They review the experimental evidence of congenital malformations produced in animals subjected to diets deficient in vitamins and conclude that the embryo requires to store vitamins in order to avoid fœtal death or congenital malformation. They also stress the need for the potential mother to have a diet adequate in vitamins, in order to facilitate embryonic requirements in early pregnancy at a time prior to its usual diagnosis. Vitamin deficiency would appear, therefore, to provide an imbalance in the complex environment. An adequate supply of vitamins, although essential, may be only one of several factors which require to be present in order to obtain normal growth. The exact mode of action of vitamin deficiency in promoting embryonic disturbances seems to be unknown. It may result in alterations in the rate and timing of cellular divisions since members of the vitamin B group play an active part in cell metabolism.

Another important phase in the formation of the mouth, which was observed, was the differentiation of its structural elements. The differentiation of the submandibular salivary gland was found to be associated with a mesenchymal condensation, an arrangement similar to that found in relationship to the developing tooth (Tonge, 1953). The work of Grobstein (1953*a*, *b*) indicates the importance of the mesenchymal condensation in relation to the developing submandibular gland. He found that the submandibular epithelial tissue would differentiate typically, only when combined with submandibular mesenchyme.

Sucking and swallowing are functions well developed at birth in all mammals, and it seems likely that the structures necessary for these functions will be developed long before they are required. In considering prenatal muscle contraction it is well to remember that the more primitive mesenchymal cells and myoblasts seen in the earlier stages were capable of deformation in several directions. Their elongation committed them to deformation in one direction. The distinction is one of degree, at first the potentiality for irregular deformation of a part, later the capacity for a regular pattern of contraction—an essential before muscular contraction can occur. At 42 days' ovulation age myoblasts with single nuclei were seen in the tongue musculature, at 47 days multinucleated cells were present. Myofibrillæ were observed in specimens of about 80 days and it is generally conceded that the capacity to respond to direct irritation precedes myofibril formation. At 117 days there is

no difficulty in demonstrating muscle fibres with well-marked cross striations. The capacity for muscle contraction is now well developed and it seems likely that the contraction of muscles in swallowing may be possible at an earlier stage, an assessment of the musculature suggests about 11–12 weeks as a possible time. Thus, by the end of the third month the pattern of mouth formation is complete; it has commenced to function, and only additive growth and some remodelling occur.

ACKNOWLEDGMENT

I should like to record my thanks to Mr. C. J. Duncan, Director of the Department of Photography, for the photomicrographs, and Mr. D. Auld for technical assistance in the preparation of the histological material.

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Marked Paget's Disease, Mainly of the Mandible, in a Woman

By WARREN HARVEY, M.R.C.S., L.R.C.P., F.D.S. R.C.S.Eng.

Introduction.—Paget's disease of the jaws is not common; for instance, the Oral Diagnosis Clinic in the School of Dentistry of the University of Pennsylvania had seen 3 cases in 50,000 admissions since 1935 (Burket, 1946). Novak and Burket (1944) reported that in 138 cases of generalized Paget's disease the maxilla was involved in 20 cases and the mandible in 3 cases. In 1945 Thoma, Howe and Wenig, from a review of the literature, found only 1 recorded case of monostotic Paget's disease of the mandible.

Case history.—A woman, aged 72, came from South America with the sole desire of seeking treatment to improve the appearance of her prominent jaw. She said that her teeth had always been difficult to extract and that her lower jaw started to get larger about six years ago; her hats were still the same size and her height had not changed. When her brother was 65 his jaw slowly increased in size.

On examination.—The teeth showed numerous carious cavities, but were firm and not spaced, and the gums were healthy.

On investigation.—X-rays showed no calcification in the suprarenals; the hands, long bones, vault and base of skull were normal. There was slight change in calcium density and the trabecular structure of the ilium and ischium near the right hip-joint was suggestive of very early Paget's disease. There was hypercementosis of the roots of the teeth in both jaws, and in the mandible there were areas of absorption and sclerosis.

The Wassermann reaction and Kahn test were negative. The serum alkaline phosphatase was 27·8 K.A. units (normal 3–13). The inorganic phosphorus was 2·4 mg.% (normal). The serum calcium was 10·2 mg.% (normal).

The radiographic evidence of concomitant osteoporosis and osteosclerosis, and the raised serum alkaline phosphatase were the significant features in the diagnosis.

The main interest of this case is that although there is such marked evidence of disease in the mandible, the rest of the body is only affected in the slightest degree, in the region of the right hip.

I am very grateful to Dr. H. W. A. Post for the X-rays and to Dr. J. H. O. Earle for the laboratory findings, and to Professor M. A. Rushton, who helped me in my dilemma as to treatment when he told me that inactivity might be masterly.

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Section of Anæsthetics

President—KATHARINE G. LLOYD-WILLIAMS, C.B.E., M.D., F.F.A.R.C.S.

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Fluoromar in Anæsthesia

By JOHN W. DUNDEE, M.D., F.F.A.R.C.S.

Lecturer in Anæsthesia, University of Liverpool

THERE have been many attempts made to improve on the original diethyl ether, but apart from Leake and Chen's introduction of the divinyl compound, there are no other ethers which have, as yet, received wide acceptance in anæsthesia. Most of the recent work on this subject is the result of systematic studies of various ethers by John C. Krantz, Jr., and his colleagues, from the University of Maryland. In 1946 they drew attention to methyl *n*-propyl ether (Krantz, *et al.*, 1946), which has sporadically received attention since, both in this country and in America. The following year they introduced ethyl vinyl ether (Krantz *et al.*, 1947), but its clinical use was not described until 1955 (Dornette and Orth, 1955; Sadove *et al.*, 1955).

Partially fluorinated ethers next attracted attention, and studies by Lu *et al.* (1953) suggested that tri-fluoroethyl-vinyl ether gave promise of being a useful anæsthetic agent. This drug, known as Fluoromar, was further investigated by Krantz *et al.* (1953) and clinical reports on its use have been published by Sadove *et al.* (1956), Gainza *et al.* (1956) and Dundee and Dripps (1957).

Table I shows the formula of Fluoromar in relation to other ethers in current use. The

TABLE I.—RELATIONSHIP OF TRIFLUOROETHYL – VINYL ETHER (FLUOROMAR) TO OTHER ETHERS USED IN ANÆSTHETIC PRACTICE

Formula	Ether
$CH_3-CH_2-O-CH_2-CH_3$	Diethyl
$CH_2=CH-O-CH=CH_2$	Divinyl (Vinesthene)
$CH_3-CH_2-O-CH=CH_2$	Ethyl–vinyl (Vinamar)
$CF_3-CH_2-O-CH=CH_2$	Trifluoro–ethyl–vinyl (Fluoromar)
$CH_3-O-CH_2-CH_2-CH_3$	Methyl *n*–propyl (Neothyl : Metropyl)

trifluorocarbon is very stable and the drug has none of the chemical properties of inorganic fluorides. There is no tendency for the vinyl grouping to hydrolyse and form acetaldehyde in contact with hot soda lime. Fluoromar is a clear colourless liquid, with a much less pungent smell than diethyl ether not unlike that of methyl *n*-propyl ether. Its oil/water solubility is 94 (3·2 for diethyl ether) and solubility in water 0·4 ml.%. The physical properties have been summarized by Sadove *et al.* (1956) and of these the inflammability range deserves special mention. While the low limit of inflammability of 4·0 vols.% is higher than that of the non-fluorinated isomer or diethyl ether, it is still well within the range used in clinical anæsthesia (3–8 vols%). The maximum spark energy for ignition is also higher than that of other ethers. In spite of the presence of a halogen in the formula, it has been shown that Fluoromar does not sensitize the heart to adrenaline. A hepatotoxic action might also be predicted from its physical properties but liver dysfunction is not any more marked after Fluoromar than after the use of other anæsthetics (Gainza *et al.*, 1956).

The course of induction of anæsthesia with Fluoromar in 287 hospitalized premedicated subjects, compared with similar cases receiving diethyl (575) or divinyl ether (115), at the same hospital by the same anæsthetists, is summarized in Table II. While the incidence of

TABLE II.—COMPARISON OF INDUCTION PERIOD IN PREMEDICATED HOSPITALIZED PATIENTS WITH THREE ETHERS

Ether	Diethyl	Divinyl	Trifluoroethyl vinyl
Incidence of smooth induction:			
(*a*) with N_2O-O_2	51%		65%
(*b*) following thiopentone	67%		75%
(*c*) open drop		65%	54%
Side effects during induction:			
(*a*) coughing	15%	4%	8%
(*b*) laryngospasm	3%	0%	4%
(*c*) excitement or muscular movement	17%	26%	11%
(*d*) excess salivation (adults only)	7%		2%
Adequate jaw relaxation during surgical anæsthesia	94%		73%

events attributable to irritant effects on the respiratory passages was lower with Fluoromar than with diethyl ether, the difference between the two drugs was not striking. The boiling point of 42·7° C. makes induction with the open drop technique difficult, as compared with divinyl ether. Of 28 cases in whom this was attempted with Fluoromar, induction was very prolonged in 7, whereas this only occurred in 4 out of 115 cases with divinyl ether. It was surprising to find that the incidence of good relaxation of the jaw muscles during surgical anæsthesia was not as good with Fluoromar as with diethyl ether. This may not be a specific effect of the drug but the result of its extremely rapid elimination, the few breaths of air taken during laryngoscopy or insertion of an airway having lightened the anæsthesia.

Once surgical anæsthesia was reached, there was a greater degree of flexibility with Fluoromar than with diethyl ether. Constant attention to the administration was necessary lest apnœa or too marked lightening should inadvertently occur. Guedel's classical planes of anæsthesia with diethyl ether were frequently inapplicable to Fluoromar. The sequence of events resembled the administration of cyclopropane in that, after morphine or pethidine as pre-operative medication, respiratory paralysis would frequently appear (Guedel, stage 3) before complete cessation of eyeball activity or loss of pharyngeal reflex (Guedel, stage 1). Electroencephalographic tracings during induction in 12 subjects showed changes similar to those described for diethyl ether. However, during established anæsthesia there was frequently some difficulty in assessing the depth from the EEG pattern. Surgical anæsthesia occurred at levels 2–3, deep anæsthesia at 4–5, while apnœa occurred between levels 5 and 7. Blood levels on 22 subjects (Dundee and Dripps, 1957), who only received atropine before induction, showed progressive depression of the central nervous system with increasing blood concentration of the drug. The range for surgical anæsthesia of 15–39 volumes per 100 ml. is similar to that found by Sadove *et al.* (1955).

Apart from effects secondary to tachypnœa, the action of Fluoromar on blood pressure and pulse-rate was similar to that of diethyl ether. However, the ease with which anæsthesia could be suddenly deepened gave the impression that hypotension was more common after Fluoromar, but the fall could be quickly reversed by lightening the depth of anæsthesia. Tachypnœa (to be discussed later), if of short duration, caused an increase in blood pressure, which could be reversed by the use of pethidine or controlled respiration. If tachypnœa was allowed to persist, the blood pressure fell after an hour or so to subnormal levels, and this sequence of events was invariably followed by moderate to severe post-operative hypotension. No disturbances in the electrocardiographic tracing were noted, save a displacement of the pacemaker during light anæsthesia, with return to normal as the depth was increased.

The respiratory rate during the use of Fluoromar is more rapid in patients who have not received morphine or pethidine before induction. In such subjects the incidence and degree of tachypnœa is about the same as for trichlorethylene. The respiratory rate increases with the duration and depth of anæsthesia, and at high rates the tidal volume is markedly depressed and respiratory acidosis occurs. As in the case of trichlorethylene, the intravenous injection of pethidine in 10–20 mg. doses abolished the tachypnœa and increased the tidal volume. Irrespective of the respiratory rate, Fluoromar was much more depressant on respiration than diethyl ether.

Abdominal relaxation was variable and was often as good as that produced by diethyl ether. Sometimes the inability to judge the depth of anæsthesia correctly led to poor operating conditions. The combination of Fluoromar with muscle relaxants was not studied in detail, but impressions suggest a synergism with the non-depolarizing drugs, such as exists with diethyl ether. Recovery from anæsthesia was always rapid and only 5 out of 280 cases, irrespective of the duration of anæsthesia, were not fully conscious within thirty minutes of the end of the operation.

The analgesic properties of Fluoromar were studied in patients undergoing operation and in volunteers. It was not as potent an analgesic as trichlorethylene, but after-effects did not

last as long. With the Cyprane inhaler at a constant setting, only eight to ten minutes' analgesia could be obtained, presumably because of cooling of the vapourizer. Recovery was not as prompt as after nitrous oxide—oxygen, and when this was used in conjunction with Fluoromar, there was difficulty in keeping the patient out of the second stage of anæsthesia. This combination proved very good for dental extractions and in premedicated hospitalized patients, but when tried in 52 unselected outpatients excessive salivation and nausea and vomiting were troublesome. Fluoromar did not prove as satisfactory as methyl *n*-propyl ether or trichlorethylene for this purpose.

A comparison of the properties of Fluoromar and its effects in man with those of other volatile agents is made in Table III. This does not reveal any outstanding advantage over

TABLE III.—COMPARISON OF SOME OF THE IMPORTANT PROPERTIES OF THE VOLATILE ANÆSTHETIC AGENTS

	Fluoromar	Diethyl ether	Divinyl ether	Methyl *n*-propyl ether	Trichlor-ethylene
Physical properties					
Irritation	±	++	+	±	±
Volatility	±	+	++	+	−
Inflammability	+	++	++	++	−
Safety with soda-lime	++	++	++	++	−
Clinical effects					
Respiratory depression	++	±	++		±
Tachypnœa	++	+	+		++
B.P. fall, deep anæsthesia	++	++	++	++	+
ECG changes	±	+		+	++
Compatibility with adrenaline	++	++			−
Rapid depth changes	++	+	++	++	±
Safety after prolonged use	++	++	−		++
Relaxation	+	++	+	+	±
Rapid recovery	++	−	++	++	−

drugs already available in British anæsthetic practice. Had it been completely non-inflammable, it would have been very useful; and had it been less easy to produce apnœa and hypotension, it might have been the drug of choice for the inexperienced or occasional anæsthetist. As it stands there does not seem any point in introducing the drug into this country.

ACKNOWLEDGMENTS

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Some Observations on Fluothane

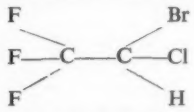
By R. BRYCE-SMITH, D.M., F.F.A. R.C.S.
First Assistant

and H. D. O'BRIEN, M.B., F.F.A. R.A.C.S.
Nuffield Dominion Clinical Assistant, Nuffield Department of Anæsthetics, University of Oxford

As our knowledge of Fluothane is still very incomplete we wish to avoid statements about its properties and behaviour which are too dogmatic, and to confine ourselves to what has been observed during the actual clinical administration of the drug in approximately 500 cases.

The investigation was begun in the middle of 1956 when Johnstone had already been using Fluothane for several months. We therefore had the advantage of knowing a little of what might be expected after reading a preliminary report which he submitted to Imperial Chemical Industries Ltd. who developed (Raventos, 1956; Raventos and Suckling, 1956) and manufactured the drug. The method of administration which he was using was also known, and through the medium of Sir Robert Macintosh who visited Johnstone at work, we received much practical advice. It is therefore obvious that Johnstone's experience is greater than ours, and any credit which may be due for the introduction of this drug into anæsthesia is his. On the other hand, if subsequent events prove that blame rather than credit is appropriate, we must accept our fair share in the knowledge that we may have furthered the popularity of this agent.

Fluothane is a clear, colourless, heavy liquid with a specific gravity of 1·86. It has a boiling point of 51° C., and thus volatilizes comparatively easily, giving off a vapour with a sweetish odour similar to that of chloroform. Chemically, it is a halogenated ethane which has the virtue of being non-inflammable and non-explosive.



It has therefore aroused the interest of the Medical Research Council Committee on Non-Explosive Anæsthetics who are independently carrying out an extensive investigation.

The first object was to administer Fluothane by the simplest means to determine the effectiveness of known concentrations of vapour, and in doing this to avoid, as far as possible, the influence of other anæsthetic drugs. Initially, therefore, we employed the open drop method of administration, and also an E.M.O. ether inhaler (Epstein and Macintosh, 1956) modified and calibrated for Fluothane. With the exception of volunteers and about 20 patients, all received some combination of premedicant drugs. In addition, the majority of our patients were induced with a preliminary injection of thiopentone.

It appeared that 1% Fluothane vapour in air was the weakest concentration capable of producing unconsciousness in an unpremedicated healthy adult. Even the prolonged inhalation of 0·5% Fluothane in these circumstances failed to cause loss of consciousness, nor indeed, any worth-while degree of analgesia. Concentrations of 2% Fluothane in air produced satisfactory surgical anæsthesia in most cases, although the degree of relaxation obtained depended to a large extent on the respiratory efforts of the patient (if these were not assisted) and, hence, the influence of other depressant drugs. Rarely was it necessary to exceed a concentration of 2%, although 3% was employed on occasions in robust subjects or where extreme degrees of relaxation were necessary.

Induction was usually rapid, smooth, and free from unpleasant subjective sensations for the patient. Coughing and breath holding were rare, and an excitement stage unusual. The preliminary injection of thiopentone seemed to reduce the incidence of restlessness and helped to provide a smoother induction. Thus, quite apart from considerations for the comfort of the patient, a "sleep dose" of thiopentone became routine before most administrations.

During the course of every anæsthetic we came to expect several characteristic features: flushing of the skin which became warm and dry; suffusion of the conjunctival vessels; and dilatation of the superficial veins of the limbs which became prominent. This occurred within a few minutes of starting the administration and was more marked than might have been expected with other forms of anæsthesia. The masseter muscles relaxed early and with depression of the pharyngeal reflexes an oral airway or a laryngoscope could be introduced. At this time, stimulation of the cords would result in closing of the glottis, possibly a cough, but not laryngeal spasm.

There was a fall in blood pressure within the first five minutes, usually accompanied by a reduction in pulse-rate. It has been suggested that Fluothane is a sympathetic-ganglion blocking agent, and the almost typical fall in blood pressure, together with the general appearance of the patient would support this view, although this has not been proved pharmacologically. In a high proportion of cases there was a fall in the minute volume accompanied by a compensatory rise in the respiratory rate. But in some volunteers, very slow rates were seen. This appears to be an individual variation which is not predictable and for which we can offer no satisfactory explanation.

After stopping the administration, consciousness returned quickly unless pre-operative medication had been heavy. We were impressed by the speed with which volunteers recovered their mental alertness, although a physical sensation of lassitude persisted for several minutes. During this time, diplopia was noticed and, not uncommonly, a marked

dryness of the mouth. On recovery, patients usually felt well and there was a minimum of nausea and vomiting. However, since there was no residual analgesia, the pain of an operation was soon felt and this effect was, of course, most marked in children who received a barbiturate for premedication. Not unnaturally this painful stimulation disturbs the patient and may cause restlessness. As soon as an analgesic was given, the restlessness ceased and emergence from anæsthesia became peaceful.

From this broad pattern of anæsthesia under Fluothane, certain features demand further attention.

Effect on the Respiratory System

As a rule, the depth of respiration decreased and the rate increased during the course of an anæsthetic. This was apparent clinically, and was often sufficient to cause cyanosis unless respiration was assisted, or oxygen added to an inspired mixture of Fluothane and air. Measurements of minute volumes were made by allowing the inspired vapour to be drawn through a spirometer, and were found to be surprisingly small. In both volunteers and patients recordings were obtained of less than 2 litres per minute after only five minutes' inhalation of 1% Fluothane in air. Such extreme degrees of depression were unusual, but it soon became obvious that an increase in the respiratory rate, even in the presence of an apparently adequate minute volume, could result in an insufficient tidal exchange.

Recently, we have attempted to reproduce Johnstone's technique of giving nitrous oxide, oxygen and Fluothane from a Boyle machine, but substituting the specially calibrated E.M.O. inhaler for the trilene bottle. The concentration of oxygen was never allowed to fall below 25%, and no cyanosis was seen in patients who received this mixture. The pattern of depressed minute volume and increased respiratory rate still persisted, and, in both groups, the effect of premedication was obvious, and confirmed our earlier opinion (Bryce-Smith and O'Brien, 1956) that light premedication with atropine alone, or pethidine 50 mg. and atropine, is preferable to the more usual mixtures containing morphine or Omnopon (*see* Table I). The response of the body to Fluothane vapour needs more careful study, and since it must be assumed that carbon dioxide retention is occurring under these respiratory conditions, a study of carbon dioxide levels is needed.

Table I.—The Effect of Light and Heavy Premedication on Minute Volume

All recordings were made after five minutes' inhalation, and demonstrate the higher proportion of low minute volumes in those patients who received Omnopon and scopolamine for premedication. There is an apparent difference between the Fluothane/air and the Fluothane/nitrous oxide/oxygen series which is difficult to explain.

Minute Volumes

	Premedication	
1% Fluothane/air	Pethidine 50 mg. Atropine 1/100 gr.	Omnopon 1/3 gr. Scopolamine 1/150 gr.
⩾ 6 litres/min.	28%	24%
3·1–5·9 litres/min.	52% } 24 cases	42% } 38 cases
⩽ 3·0 litres/min.	16%	34%
1% Fluothane, N_2O, O_2		
⩾ 6 litres/min.	23%	9%
3·1–5·9 litres/min.	37% } 30 cases	27% } 33 cases
⩽ 3·0 litres/min.	40%	62%

Under Fluothane/air anæsthesia, respiration is usually smooth, quiet and regular. The vapour is not irritating to the respiratory tract and respiration can usually be controlled with the greatest of ease at light levels of anæsthesia.

In experimental work on dogs, and in patients who received Fluothane/air only, periods of apnœa lasting for one to two minutes sometimes occurred during induction. These were never seen after induction with thiopentone, nor have they been apparent in patients who received the thiopentone, nitrous oxide, oxygen, and Fluothane mixture. This apnœa did not appear to be related to the concentration of vapour administered, and was not a response to a high concentration which might have caused laryngeal spasm. Inflation could still be performed with ease, and spontaneous respiration usually re-started after applying a painful stimulus.

Effect on the Cardiovascular System

The effect of Fluothane on the rate and rhythm of the heart has already been the subject of an intensive electrocardiographic study (Johnstone, 1956). We have detected no cardiac arrhythmias during Fluothane anæsthesia, but bradycardia occurred almost routinely. Even the administration of clinical doses of adrenaline (up to 0·5 mg.) caused no more than a temporary and brief increase in the pulse-rate.

Falls in blood pressure were common, and the degree of hypotension seemed to be related to the concentration of Fluothane vapour. In very few cases, however, were these falls of an alarming extent, and even when they did occur the general condition of the patient remained surprisingly good. Indeed, from the warm dry skin, and the strong pulse which could be felt at any of the classical points for palpation, it was hard to believe that any fall in blood pressure had occurred.

The blood pressure and pulse-rate tended to follow each other closely, and a rise in pulse-rate was nearly always followed by a rise in blood pressure. Thus we have come to place more reliance on atropine as the antidote to hypotension than on such agents as methyl amphetamine and ephedrine.

There was little to choose between the effect of Fluothane/air, and Fluothane, nitrous oxide, and oxygen on the blood pressure. The maximum and average falls of blood pressure in both groups were comparable, although the average fall with the higher concentrations of Fluothane (1·5–2·0%) was slightly greater in the Fluothane/air series (Table II).

TABLE II.—THE EFFECT OF DIFFERENT CONCENTRATIONS OF FLUOTHANE ON THE BLOOD PRESSURE

The average fall under 1% Fluothane is not alarming, but becomes appreciable with 1·5% and 2%. In a few instances, there was a rise in blood pressure (listed under minimum fall), and with 1% Fluothane, a reasonable number of cases showed no fall at all.

	Blood Pressure Falls (mm.Hg systolic)		
	Fluothane/N_2O/O_2		
	1%	1·5%	2%
No. of cases	28	8	6
Max. fall	75 (from 140)	100 (from 160)	70 (from 140)
Min. fall	+30	+10	10
Average fall	15	29	27
No. with no fall, or a rise in B.P.	11	3	1
	Fluothane/air		
No. of cases	42	12	16
Max. fall	70 (from 140)	75 (from 180)	75 (from 180)
Min. fall	+10	+10	5
Average fall	21	39	36
No. with no fall, or a rise in B.P.	10	1	0

All patients received thiopentone 0·25 gram for induction.

THE USE OF MUSCLE RELAXANTS WITH FLUOTHANE

Succinylcholine chloride has been administered to 101 patients under Fluothane anæsthesia. The effects appeared to be identical to those seen when this muscle relaxant is used with other anæsthetic agents.

43 patients have received gallamine triethiodide and in some there have been slight falls in blood pressure. However, the extent of these falls has been no more than might be expected with Fluothane by itself. In at least half of the cases, there was, in fact, a slight rise in blood pressure, coinciding with the rise in pulse-rate which is characteristic of gallamine.

d-tubocurarine chloride has been administered to 35 patients, but here the effect on the cardiovascular system tended to be more dramatic than with gallamine triethiodide. Falls in blood pressure were more common, and frequently more profound, but provided the concentration of Fluothane administered did not exceed 1%, there has been no cause for serious alarm.

We are of the opinion that the non-depolarizing muscle relaxants should be used cautiously in conjunction with Fluothane. In particular, there is a risk of serious hypotension when *d*-tubocurarine is administered in the presence of bradycardia. We must warn most strongly against the injudicious use of neostigmine. We believe that a preliminary injection of atropine should be made at least five minutes before the neostigmine is administered, and that the dose should be of the order of 1/75–1/50 grain. Neostigmine is best given in divided doses, never more than 1 mg. at a time, and the total dose not exceeding 2·5 mg. With less cautious dosage there may be a calamitous slowing of the pulse-rate.

These reactions to gallamine, *d*-tubocurarine, neostigmine and atropine are interesting, and when considered in relation to the appearance of the patient, the bradycardia, and the hypotension under Fluothane alone, suggest that this drug must exert some influence on the sympathetic nervous system. Since there is evidence that this does not occur at the ganglia, then it may well be that the action is more peripheral.

Miscellaneous Observations

Diplopia and dryness of the mouth have already been mentioned as not unusual features during the immediate recovery period. In addition, bouts of shivering lasting for five to ten minutes have been seen before consciousness has fully returned. The shivering appeared to be aggravated by any stimulation of the patient, but was seen less commonly when nitrous oxide, oxygen and Fluothane was used than Fluothane/air.

Unfortunately, the administration of Fluothane demands a very careful control of the concentration of vapour. Thus, most existing anæsthetic apparatus in its present form is unsuitable for the administration of the drug. The difficulty is further increased by the knowledge that Fluothane, in the presence of moisture, can attack tin and aluminium. Considerable difficulty was experienced before the E.M.O. inhaler could be modified for use with Fluothane without undergoing corrosion and, in consequence, jamming of moving parts.

Conclusion

It is too early yet to pass judgment on Fluothane, but we believe that this agent merits a place in the anæsthetist's armamentarium. Non-inflammability, ease of administration, flexibility, smooth and rapid induction, quick recovery with a minimum of after-effects, and a bloodless surgical field, are advantages which cannot be dismissed lightly. On the other hand, depressed respiration, hypotension and bradycardia have sinister implications unless they are controllable and reversible. Further, they may be fatal unless recognized. Other disadvantages undoubtedly exist of which we have little or no knowledge, and until the investigations of the Committee of the Medical Research Council and others have been completed, the use of Fluothane should be limited and cautious.

While we think that Fluothane is an improvement on ethyl chloride either as a sole anæsthetic or as an induction agent to ether, and by virtue of its flexibility could replace trichlorethylene in a nitrous oxide/oxygen sequence, to mention but two possibilities, we would be unwilling to make widespread recommendations for its use at present. It would be regrettable if such a promising drug acquired a bad reputation early on, due to ignorance of its properties and of the correct method of usage.

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Dr. M. Johnstone: I have now administered Fluothane to over 1,200 patients, using the technique already described (Johnstone, 1956). With the 1% (approx.) vapour concentration the induction, maintenance, and recovery from anæsthesia have been delightfully smooth in each patient. Spontaneous respiration has persisted in all patients and significant degrees of respiratory depression have been uncommon, presumably because I do not use morphine or its analogues as premedicants. Increased respiratory rates are common during Fluothane anæsthesia but seldom of a degree requiring an adjustment of the technique.

Muscular relaxation has been adequate in all cases except in a proportion of the laparotomies; it has not yet been attempted to obtain further relaxation in the latter by increasing the Fluothane concentration. Roughly speaking, Fluothane 1·5% provides about 80% of the relaxation needed for an upper abdominal operation; the remaining 20% of the relaxation, required only during the initial exploration and the final closure of the peritoneal cavity, can be obtained with small doses of suxamethonium (30 mg. to 50 mg. intravenously). Longer-acting relaxants, particularly of the competitive type are not required and are probably contra-indicated for the reasons already mentioned (Johnstone, 1956).

As far as I can tell, disturbances of cardiac rhythm are practically non-existent during Fluothane anæsthesia in efficiently ventilated and adequately atropinized patients. Small hæmostatic doses of adrenaline (up to 20 c.c. of a 1/150,000 solution of adrenaline hydrochloride injected subcutaneously) have failed to cause any disturbance of cardiac rhythm in adults anæsthetized with Fluothane. I have observed a multifocal ventricular tachycardia following the filling of a congested bladder with about 400 c.c. of a 1/100,000 solution of adrenaline hydrochloride during a cystoscopic examination of a patient under Fluothane anæsthesia; the arrhythmia was abolished immediately by the insufflation of ether vapour and recovery was uneventful. The hypotensive effect of Fluothane is minimal with the 1% vapour concentration required for the maintenance of anæsthesia, provided atropine is given in adequate doses, the blood volume is maintained within reasonably normal limits, and postural influences are controlled.

Post-operative nausea and vomiting have been absent in over 95% of my patients after Fluothane

anæsthesia. On one point I am certain: the overall picture of the post-operative condition of the patients has been incomparably better than after any other anæsthetic technique I have ever used. An outstanding feature has been the complete absence of the shock syndrome after surgery under Fluothane anæsthesia. At the moment it is not possible to explain this effect but I feel certain it is related to the unusual pharmacological effects of Fluothane on the autonomic nervous system (Raventos, 1956), effects which are fundamentally different from those of any other volatile anæsthetic agent.

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Dr. B. W. Peckett: Mr. Bernard Johnson and I have been giving a clinical trial to Fluothane at the Middlesex Hospital for the last three months. We have now anæsthetized nearly two hundred patients with a thiopentone, nitrous oxide, oxygen, Fluothane sequence using a Boyle's apparatus with Fluothane in the trilene bottle (1–2% Fluothane concentration was used).

Our impressions have been very favourable. It is easy and non-irritant to administer. Relaxation of the jaw occurs early, allowing insertion of the airway almost immediately. Relaxation is good and can be potentiated by the addition of any of the common relaxants. *d*-Tubocurarine chloride and Fluothane together generally cause hypotension, which is rarely severe. It appears to be safe with small quantities of adrenaline injected subcutaneously, but this requires further investigation.

Its worst feature is the often occurring, rapid, shallow respiration with marked falls in minute volume, but respiration can and should be assisted under these circumstances. It is very easy to control respiration completely.

Vomiting is mild following Fluothane, but it does occur.

We feel that Fluothane deserves a prolonged clinical trial and may well prove the best agent to use in the presence of diathermy, particularly for short procedures requiring moderately deep anæsthesia; and for operations where bleeding may be a great inconvenience to the surgeon, such as plastic operations, radical mastectomies, thyroidectomies and many E.N.T. operations.

Dr. H. J. Brennan: I have seen an alarming degree of bradycardia and hypotension in two healthy male adults premedicated with papaveretum and hyoscine—a condition immediately corrected by the intravenous injection of atropine sulphate. Hyoscine does not provide sufficient cardiac protection against Fluothane, and I regard adequate premedication with atropine as essential.

Dr. T. Cecil Gray: Fluothane appears to possess every property we consider bad in an anæsthetic drug: Tachypnœa combined with reduction in tidal volume, hypotension and sensitization of the heart to adrenaline are all extremely undesirable effects which the speakers have assured us are produced by this drug, and yet, to a man, they still regard it as a valuable agent!

It is probable that the facts that it is non-explosive, non-inflammatory and produces rapid induction and recovery of anæsthesia will give it a small niche in anæsthetic practice but I find it difficult to conceive that it will replace any of the agents at present at our disposal.

The whole trend of anæsthesia is to avoid the blunderbuss type of anæsthetic agent and to use drugs with as few side actions as possible, in order to achieve specific ends such as relaxation and hypotension. I hope that this is a principle that will not be easily abandoned.

Dr. L. Rendell-Baker: Though I agree that Fluothane opens a new and interesting avenue for research, I feel that the great frequency with which it produces bradycardia and hypotension often combined with marked diminution of the patient's tidal exchange hardly marks it as an ideal anæsthetic agent. The incidence of nausea and vomiting with Fluothane has certainly not been less than is commonly experienced following other agents such as trichloroethylene, for example. With some of the cases, vomiting has been troublesome.

Section of Obstetrics and Gynæcology

President—R. A. BREWS, M.D., M.S., F.R.C.S., F.R.C.O.G.

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Some Clinical Aspects of Developmental Anomalies of the Female Genito-urinary Tract

PRESIDENT'S ADDRESS

By R. A. BREWS, M.D., M.S., F.R.C.S., F.R.C.O.G.

THIS address is based upon case records for the past sixty years and autopsy reports for the past forty years at the London Hospital.

Gynatresia with cryptomenorrhœa	83 cases
Incomplete vaginal septa	17 cases
Duplication of genital tract without cryptomenorrhœa:	
Symmetrical	32 cases
Asymmetrical	12 cases
Other abnormalities of the genital tract	16 cases
Selected anomalies of the urinary tract	5 cases
Found at autopsy	35 reports
	200

In addition to commenting upon these 200 cases from the London Hospital, others are referred to which have come under my care in different hospitals during the recent half of this period.

GYNATRESIA WITH CRYPTOMENORRHŒA

83 cases of cryptomenorrhœa resulting from a developmental obstruction distal to menstruating endometrium are included in the series and in Table I they are grouped into clinical types:

TABLE I.

Occluding membrane at the vaginal orifice	
Hæmatocolpos. Simple 54, Double 1	55
Hæmatocolpos (H-C) and hæmatotrachelos (H-T)	1
H-C, H-T and hæmometra (H-M)	3
H-C, H-T, H-M and hæmatosalpinx (H-S)	3
Occlusion at a higher level	
In the vagina: vault H-C ±H-T, H-M and H-S	2
In the cervix: H-T ±H-M and H-S	5
Unilateral occlusion in a double genital tract	
In the vagina: vault H-C ±H-T, H-M and H-S	7
In the cervix: H-T ±H-M and H-S	1
In the corpus: H-M ±H-S (menstruating accessory horn)	6
(*Infection of retained menstrual debris*—5)	83

The clinical features of simple hæmatocolpos are well known but a few points have emerged from a study of the 54 cases in this series. About half of them came under medical care because of difficulty in micturition or retention of urine. One-third complained of pain, in many cases typical of dysmenorrhœa, but in others, of a dull aching character above the pubes or in the sacro-perineal region, aggravated by sitting or by defæcation and probably due to vaginal distension. The remainder presented in a variety of ways, complaining of such things as abdominal swelling, hæmorrhoids, or anxiety because of delayed onset of periods, and initial diagnosis included appendicitis and ruptured ectopic pregnancy. One girl of 15 years fell on her perineum and, in doing so, ruptured a hæmatocolpos with embarrassing social consequences. The age incidence ranged from 12 to 24 years and 5 of these girls were 18 or older.

The only case of double hæmatocolpos was admitted under Dr. A. H. N. Lewers in 1907. A single girl of 17 years, she had never menstruated and a sudden retention of urine brought her to hospital. After catheterization a tense abdomino-pelvic swelling reached from the perineum to just above the pubes. The external genitalia were well developed but there was no vaginal opening. Dissection at its normal site opened two vaginæ distended with tarry fluid and with a separate cervix at each vault.

In 7 further cases of hæmatocolpos due to a low vaginal atresia distension also involved the genital passages at a higher level. In 1 the cervix alone was affected (hæmatotrachelos), in 3 the uterine body as well (hæmometra) and in the remaining 3 cases the fallopian tubes were also affected (hæmatosalpinx). Involvement of the uterus and fallopian tubes does not depend upon the size of the hæmatocolpos. The largest in the series contained 4½ pints and in this case the uterus and fallopian tubes were not distended, whereas both were grossly distended in an instance where the hæmatocolpos contained only 10 oz. Apart from palpable enlargement of the tubes, there must be many cases where a little fluid finds its way back along them to the peritoneal cavity. Again, dilatation may have involved the upper genital tract even when symptoms are of very short duration. One girl of 13 years with pain of one month's duration had already developed a hæmatotrachelos and a hæmometra. Another girl of 12 years with pain of less than twenty-four hours' duration in the right iliac fossa had her abdomen opened through a grid-iron incision, the pre-operative diagnosis being acute appendicitis. She proved to have a hæmatocolpos, hæmometra and a ruptured right hæmatosalpinx with free chocolate fluid in the peritoneal cavity. The occurrence of cases of this sort make it imperative that the drainage of a hæmatocolpos should be regarded as a surgical emergency. This drainage, by crucial incision or circular excision of the membrane, would seem a minor surgical procedure; nevertheless, mishaps may occur. The first patient in this series from 1896 died under the anæsthetic before the operation could be started. In 1907 excision of an unusually thick membrane was followed by a vesico-vaginal fistula which had to be secondarily repaired. In two instances, referred to later, post-operative infection involved the genital tract.

The occluding membrane varies considerably in thickness, in its precise situation and, possibly, in embryological origin. Many conformed to the clinical description in that they bulged at the vaginal orifice and were sufficiently thin and translucent to show the dark colour of the retained, altered menstrual fluid. In other cases the membrane was flat, up to half an inch in thickness and of the same colour and appearance as the surrounding vulval tissue. The hymen was frequently to be seen below the obstructing membrane but sometimes it could not be demonstrated as a separate entity, even when carefully looked for. In one case (1929) biopsies of both the hymen and the occluding membrane were taken for histological examination. The hymen was lined on both surfaces by thick, stratified epithelium. The membrane was lined on its outer surface by similar epithelium but on the inner surface the epithelium was much thinner and of a more transitional type. Between the epithelial layers many membranes contained muscle as well as collagen fibres and in some the inner lining was a high columnar epithelium.

In 7 cases the gynatresia was at a higher level than the vaginal orifice at varying levels in the vagina and cervix. 2 of these cases, in which the vagina was completely absent, are of particular interest. In one (1895) a girl of 19 was under observation for a year for recurrent monthly attacks of severe hypogastric and low back pain. At first the uterus, on rectal bimanual examination, appeared to be of normal size, but, later, it enlarged to the size and consistency of a 10 weeks' pregnancy. There was no vaginal orifice and, with a sound in the urethra and a finger in the rectum, no vagina could be felt. After dissecting about 1½ in. upwards in the cellular plane between the urethra and the bladder in front and the anal canal and rectum behind, two bulges in the depths of the wound appeared to represent distended cervices. Each was penetrated separately with sinus forceps by Hilton's method and each drained a considerable quantity of typical retained menstrual fluid. Convalescence

was mildly febrile for five weeks, during which time the cavity was first packed with iodoform gauze and then regularly dilated. A follow-up note stated that a vagina 2½ in. deep resulted, menstruation was normal and the uterus now felt quite small. This case would appear to have been one of double hæmometra in a septate bicollis uterus with a complete atresia of the vagina.

In the other case (1909) a girl of 17 years had had monthly attacks of pain in the lower abdomen and thighs for two and a half years. Two abdominal swellings were felt, one central and sub-umbilical, the size of a fœtal head at term, the other a fixed mass in the right iliac fossa. On rectal examination a thin fibrous cord could be felt where the vagina should have been. Laparotomy disclosed a small hæmometra (2 oz.) and large bilateral hæmatosalpinges (each 10 oz.). There were many adhesions. Subtotal hysterectomy was difficult; the right ureter crossed behind the cervix to the left side. The patient developed ileus and died on the eighth post-operative day.

Simple hæmatocolpos complicated by infection.—Three examples of this condition occurred in this series. In 1933 a patient of 25 years was sent to hospital with a six days' history of abdominal pain and difficulty in micturition. A tender swelling reached to the umbilicus. Excision of a low occluding vaginal membrane released a large quantity of foul-smelling blood-stained fluid which, on culture, grew an anaerobic Gram-positive coccus. In this case the infection of the hæmatocolpos preceded surgical intervention. In 1907 another patient attended hospital with a minute opening in an occluding low vaginal membrane and the vagina filled with foul pus. The membrane had been perforated and a hæmatocolpos drained with a trochar and cannula twelve months previously. A third case in 1911 was the girl who ruptured her hæmatocolpos by falling on her perineum. The rupture closed down and there was inadequate drainage of offensive, infected menstrual debris.

Unilateral Gynatresia with Unilateral Cryptomenorrhœa

There are 14 examples of this anomaly occurring with equal frequency on either side. In every case unimpeded menstruation occurred from the unaffected side. The atresia was at varying levels but in no instance was it very low down. In 5 cases a shorter vagina was intimately related to one side of the upper part of the fully formed vagina. In 4 cases this anomaly was on the right side and in 1 case on the left. Lower abdominal and pelvic pain led to the discovery of an abdomino-pelvic swelling in each case. In 3 the initial diagnosis was broad ligament cyst and in another it was tubercular salpingo-oophoritis. In 2 cases the retained menstrual fluid amounted to 2 pints; one of these patients died of post-operative peritonitis; the other has since had 6 children. In 1 patient, aged 15 years, there was no vagina on the affected side and the cervix was occluded at the level of the os externum. She developed a large right-sided hæmatotrachelos which was drained by vaginal trachelotomy. She has since had one successful pregnancy and is again 4 months pregnant at the present time. Both these pregnancies relate to the unaffected left genital tract.

In 6 cases there was a single vagina and cervix. The unilateral atresia consisted of occlusion of a rudimentary or accessory horn. The age range of these patients was wide and the majority were, perhaps, unexpectedly old. The ages at the time they received surgical treatment were 15, 17, 20, 28, 33 and 39 years. Initial diagnosis included ruptured ectopic pregnancy, Dietl's crises, intractable dysmenorrhœa and degenerating fibroid. All had abnormal pelvic physical signs, usually a tender, irregular uterine enlargement or a tubo-ovarian swelling. In 5 cases the abnormal horn was excised. In the patient aged 39 years a total hysterectomy was done.

Imperfect drainage of one side of a double genital tract with consequent infection.—In addition to the case that developed post-operative fatal peritonitis there were 2 cases of infection consequent upon imperfect drainage of one side of a double genital tract.

(1) A single girl of 21 years gave a history of a post-menstrual, very offensive, fæcal smelling, pale green discharge since her periods began at the age of 14 years. Repeated tests at a Venereal Disease Clinic were negative for such types of infection. Careful examination under anæsthesia defined a soft swelling adjacent to the right anterior part of the vaginal vault. Pressure in this region caused fæco-purulent pus to exude from the cervical canal. It was then discovered that an antero-posterior septum divided the cervix and that ¾ in. above the lower extremity of the right-sided canal a fistulous track led into an infected sac related to the right vaginal fornix. Through an incision in the right fornix around the side of the cervix the fistulous track was excised and the infected sac laid open and marsupialized into the right fornix. The discharge subsequently cleared up. Because of the resemblance

of many features of this case to those of the following one, the sac was probably produced by infection of an incompletely developed right-sided vagina.

(2) A girl of 14 years was referred to me because of an offensive intermenstrual discharge so overpowering that on several occasions she was sent home from school on account of it. She was placed on the waiting list for admission to hospital for examination under anæsthesia and other investigations, but pain in the right iliac fossa associated with pyrexia developed and admission to the general surgical side of another hospital was arranged. The abdomen was explored for what was now a subacute lower abdominal infection and a right-sided purulent salpingitis was found. The appendix was removed and the wound was drained. The pus grew *Bact. coli* on culture and appropriate chemotherapy was instituted. The infection subsided but two months later she was admitted to hospital with a tender mass in the right iliac fossa and complaining of some foul green vaginal discharge. Vaginal examination under anæsthesia now identified a very small sinus to the right of the portio vaginalis of the cervix. The mass in the right iliac fossa felt bimanually was larger than the uterus and pressure on it caused pus to exude from the sinus in the right vaginal fornix. A further, more extensive laparotomy now revealed a right-sided pyosalpinx and pyometra which were removed at the level of the cervix. A left-sided uterine body with the left fallopian tube and ovary appeared healthy. A ureteric catheter was introduced through the cervical canal of the stump remaining after the right uterus had been removed and a subsequent X-ray showed it to be coiled up in a cavity related to the upper half of the right side of the vagina. Dissection into this from below opened a right-sided pyocolpos which was widely drained. This girl had no kidney on the right side. She has had a satisfactory convalescence and is now menstruating normally from the left uterus.

Before leaving the subject of simple hæmatocolpos I shall refer to one case of hydrocolpos which I encountered at another hospital. A girl of 15 was referred to me on the same day that she developed acute retention of urine as the first symptom of what appeared to be a classical fairly large hæmatocolpos. There was nothing suggestive of infection or toxæmia. On incising the occluding membrane, which bulged at the vaginal orifice, 40 oz. of inoffensive creamy-white fluid escaped. This fluid was sterile and contained cellular debris, many squamous epithelial cells and a small number of leucocytes. She made a straightforward, afebrile convalescence and started to menstruate normally six months later. Maliphant (1948) published a report of a very similar case He pointed out that of the small number of cases reported, more have occurred in the neonatal than the pubertal age group. Such remarkable cases give rise to conjecture. Does this fluid represent a form of so-called "white menstruation" where the endometrium is not being subjected to, or does not respond to the influence of a hæmorrhagic factor, or does it represent an accumulation of non-menstrual secretion? Perhaps, in many cases of gynatresia, a quantity of such fluid has accumulated before true menstruation begins. If this is so, then there is a case for the excision of an occluding membrane without delay, should it be discovered before puberty.

There still remain the many anomalies of the genital tract where there is no cryptomenorrhœa. In these there is no gynatresia distal to menstruating endometrium. Their importance lies, perhaps, more in their effect on child-bearing and in their not infrequent association with anomalies of the urinary tract than in their symptomatology.

Incomplete transverse or longitudinal septa may modify the internal contour of the vaginal canal. Eleven transverse and six longitudinal septa of this incomplete type found in nulliparous patients are included in this series. In some instances they were identified as the cause of dyspareunia or post-coital bleeding. In the remainder they were discovered only when a vaginal examination was made antenatally or in the investigation of unrelated complaints. Some were dilated or divided and others were obliterated or disrupted in labour. In no instance did a septum materially modify the course of labour or occasion troublesome intrapartum or postpartum hæmorrhage or, in splitting, initiate serious laceration. There is no doubt that many septa of this type escape recognition before a first confinement and are largely obliterated by it. In one of these cases a patient in labour at term had a septum across the vaginal orifice, complete except for an opening near its centre which would just give passage to a medium-sized catheter.

Duplications of the genital tract represent failures or defects in the union between the bilateral components of the utero-vaginal canal. A median septum between the two sides is a transient feature of normal evolution but it may persist in varying degrees. Fusion between the uterine parts of the Müllerian ducts may have failed, again in varying degrees, from above downwards. Many terms have been coined in the literature to describe all these variants and the classification suggested by Monie and Sigurdson in 1950 has much to com-

mend it. "Didelphian" is defined by the Shorter Oxford English Dictionary as belonging to the subclass Didelphia of the class Mammalia, characterized by a double uterus and vagina and comprising the single order of Marsupials. Actually the formation of the genital tract varies in different species of marsupials; in some there is a medial vagina with two lateral canals.

In this series there are 20 instances of double vagina and uterus found in nulliparous patients. The anomaly was found once by the patient herself and in the remainder during pelvic examination. A few of the patients had complained of dyspareunia but the majority had no symptoms referable to the condition. 11 were under hospital supervision for a total of 20 pregnancies. 4 of these pregnancies ended in spontaneous miscarriage (20%), 6 were terminated by elective Cæsarean section near term (4 vertex and 2 breech presentations) and in the remaining 10 satisfactory vaginal delivery took place. In 6 the fœtus presented by the vertex and in 4 by the breech. All the infants were healthy and survived, the largest weighing 7½ lb.

In only one instance did the intervaginal septum persist after a first vaginal delivery and in this case the infant weighed only 4½ lb. In all the other cases the septum was either divided with scissors or disrupted itself in the second stage. In one case the upper half of the septum disrupted itself during breech delivery and a double footling presentation ensued, one leg coming down through each vaginal orifice. Progress was delayed until the lower part of the septum, on which the fœtus was seated astride, was divided with blunt-ended scissors.

The patient who discovered the anomaly herself was a generally trained nurse and midwife. When trying to insert a Tampax she found she had a double vagina. She was in the Far East at the time of her first pregnancy and was delivered by Cæsarean section partly because of the anomaly and partly because the presentation was a breech and several attempts to perform external version had failed. When home on furlough she sought advice as to whether it would be possible for her to have a natural labour. The situation was assessed and the vaginal septum was divided by cutting diathermy. Subsequently she had a successful vertex delivery and on the fifth day of the puerperium passed a decidual cast from the non-pregnant uterus.

One of my own cases, not included in this series, presented in her second pregnancy with a double vagina with the cervices fused medially. Her first delivery was by Cæsarean section because of a breech presentation. This pregnancy was in the left uterus. In her second pregnancy palpation and Lipiodol hysterogram confirmed it as being in the right uterus and delivery was by a further Cæsarean section.

The lesson to be learned from these cases is that vaginal delivery presented no serious difficulty or complication and, therefore, resort to Cæsarean section in such cases should not be made too readily.

Partial or complete duplication of the corpus uteri in association with a primarily single cervix and vagina constitutes a somewhat different clinical problem. The condition gives rise to no symptoms and the diagnosis is much more easily overlooked than when the vagina and cervix are double. Of the 11 cases in this series 6 were recognized in association with pregnancy. 2 of these were diagnosed antenatally and in both the presentation of the fœtus and labour were normal. In 2 the diagnosis was made after delivery, in 1 during manual removal of the placenta and in the other by abdominal palpation. The remaining 2 were diagnosed at laparotomy, in 1 for a tubal ectopic pregnancy and in the other for termination of a fifth pregnancy in a woman with severe morbus cordis.

I have had one case elsewhere, a young primigravida, with a persistent transverse lie which could not be corrected by external version. Delivery by Cæsarean section revealed a markedly bicornuate uterus with the fœtal head in one cornu and the breech and placenta in the other. A postnatal hysterogram confirmed the bicornuate shape of the uterine cavity.

In the absence of pregnancy the discovery of this anomaly has been very largely fortuitous as in (1) a grand multipara with procidentia, (2) a patient with carcinoma of the body of the uterus, and (3) a patient who sustained a separation of the symphysis pubis in labour. In the first and third of these cases a Lipiodol hysterogram was done and in the second it was recognized at laparotomy.

Many minor degrees of bicornuate uterus not included in this series have been revealed by Lipiodol hysterogram carried out in the investigation of infertility, spontaneous miscarriage and other gynæcological conditions. One, exceptionally pronounced, was found in a woman who had had four normal confinements without the condition having been suspected.

In reviewing this material I have been impressed by the infrequency of any association between recurrent abortion and a degree of septate or bicornuate uterus that might justify a plastic operation designed to create a uterus simplex. This was considered in one patient who had had three spontaneous miscarriages, but she was not anxious to submit to such an operation and was not pressed to do so.

Asymmetrical Duplications of the Genital Tract

My attention was directed particularly to these anomalies when I made a survey of the autopsy material accumulated by the Bernhard Baron Institute of Pathology at the London Hospital, where records are available since 1907.

Autopsies on female subjects (1907 to 1955)	11,362
Anomalies found:	
(1) Asymmetrical	
Unilateral uterus	13
Accessory horn	2
Rudimentary horn	2
(2) Symmetrical	
Bicornuate uterus	9
Arcuate septate uterus	1
Double uterus and vagina	2
(3) Agenesis	
Complete	1
Uterine	1
Incidence—1 in 366 autopsies.	31

These figures suggest that asymmetrical uterine anomalies are at least as common as the grosser symmetrical ones and, as they appear to be diagnosed less frequently, it is probable that they more often escape recognition.

Of 12 cases in the clinical series, 7 were associated with pregnancy. Five pregnancies were in the well-developed uterus. Two of these had breech presentations and were diagnosed at Cæsarean section, one had a laparotomy when an ovarian tumour was diagnosed obstructing the descent of the head into the pelvis, one had an abdominal hysterotomy and another had a laparotomy for an ovarian tumour which proved to be an ectopic pelvic kidney. The other two pregnancies were in the imperfectly developed side, one in a ruptured accessory horn and the other in a ruptured fallopian tube.

Of the 5 cases unassociated with pregnancy 4 were diagnosed at laparotomy carried out when lower abdominal or pelvic pain led to the discovery of an irregular uterine enlargement attributed in 3 cases to the presence of fibromyoma. In 1 case there was no lump but at laparotomy a cornu solidarius was found. The remaining case was diagnosed when a Lipiodol utero-salpingogram was carried out during the investigation of infertility. The diagnosis was confirmed when an intravenous pyelogram revealed only one secreting kidney on the same side as the unilateral uterus.

One of the Cæsarean sections was carried out in rather unusual circumstances. The patient, a doctor's wife, was found to have a breech presentation at 32 weeks but all attempts at version failed. She was a primigravida aged 22 years. X-ray pelvimetry showed a gynæcoid pelvis at the lower limit of normal as regards size. The fœtus did not appear to be unduly large so breech labour at term was decided upon. Labour was slow, the membranes ruptured early and the two feet came down to the vulva through a rather thick, incompletely dilated cervix. Lower segment Cæsarean section at this point revealed a left unilateral uterus which had been unsuspected. Both kidneys were normal to palpation.

This and other cases raise the question of the relationship between asymmetrical development of the genital tract and asymmetry in the development of the urinary tract. In the 17 cases found at autopsy:

Kidney absent on side of Müllerian agenesis	8
Both kidneys present and normal with complete unilateral Müllerian agenesis	2
Kidneys not specifically recorded	3
Both kidneys present and normal in 1 case of accessory horn and 1 case of rudimentary horn	2
Kidneys not specifically recorded	2

Among the clinical cases there were 16 other developmental anomalies of the genital tract:

Complete absence of vagina with rudimentary uterus. (Additional to one case associated with bilateral hæmometra already described)	9
Two-inch vagina, no uterus, no left kidney	1
Upper two-thirds vagina absent, no left kidney	1
Absent vagina with small left non-functional unicornuate uterus	1
Vaginal anus (congenital recto-vaginal fistula)	4

Selected Anomalies of the Urinary Tract

I have included 5 cases in this series where the anomaly is dominantly one affecting the urinary tract but I think it will be agreed that in each instance there is a particular obstetrical or gynæcological associated interest.

2 of these cases had *unilateral pelvic kidneys*. In 1 a pelvic lump was discovered during labour below the presenting part and obstructing delivery. Its nature was only recognized following a Cæsarean section. The other case presented in 1954 and the relevant features are as follows:

At the age of 16 years the patient had a spinal fusion performed for the treatment of a severe scoliosis. At the age of 21 she married. At the age of 25 years she attended the Out-patient Department because of infertility and right-sided lower abdominal pain. A pelvic tumour was felt somewhat to the right of the mid-line and near the pelvic brim. It was rather tethered and was thought to be an ovarian neoplasm with, perhaps, some degree of torsion of its pedicle. Laparotomy revealed that it was, in fact, a right-sided pelvic kidney with renal arteries arising from the common iliac and internal iliac arteries. The pelvis, as is usual in such kidneys, was lateral in position. The right cornu of the uterus was rudimentary but the left was well developed.

At the age of 26 years she had a quick, straightforward breech delivery from her left unilateral uterus. The kidney was palpable below the presenting part early in labour but the extending breech came down past it and labour was, therefore, allowed to continue. The infant weighed 6 lb.

Two further cases were found at autopsy, being unrecognized during life. In an adolescent girl the right kidney was situated in the false pelvis and the left in the upper true pelvis. The right cornu of the uterus was accessory and did not communicate with the developed left side. She died thirteen months after a road accident as a result of sepsis engendered by extravasation from the injured pelvis of the right kidney. The other subject had a left kidney situated in the false pelvis. Death at the age of 22 years was due to congenital morbus cordis.

A fifth case is warded at the present time. Her first pregnancy in 1946 was complicated by antepartum hæmorrhage, an oblique lie and the presence of a cystic swelling the size of an orange in front of the promontory of the sacrum. She was delivered by Cæsarean section when the presence of a placenta prævia was confirmed. The presacral swelling was retroperitoneal and extended to the right with the common iliac vessels crossing it laterally. It was thought to be a broad ligament cyst and was not removed. The patient is now pregnant again—about 22 weeks—and a cystic swelling lies in front of the upper sacrum. An intravenous pyelogram shows no sign of a renal shadow in the right loin. Catheterization of the right ureter produced a rapid flow of 35 c.c. of urine, and the diagnosis of a right-sided pelvic kidney is now a near certainty.

I have had another case at a different hospital: A single girl of 22 years, an identical twin, with a long-standing rheumatic carditis causing mitral stenosis and aortic incompetence, developed a right-sided pyelitis complicating a first pregnancy of 28 weeks' duration. At 34 weeks she further developed a severe progressive pre-eclamptic toxæmia and heart failure. The blood pressure was 160/90, there were 10 parts of albumin in her urine and she had massive œdema including the vulva. The presentation was a breech. After a short period of treatment she was delivered by Cæsarean section with sterilization. The uterus was right unilateral with a rudimentary left cornu. The right kidney was large and the left kidney apparently absent. She made a satisfactory convalescence and it became possible to investigate her genito-urinary anomaly more fully. The left kidney was situated in front of the 5th lumbar and 1st sacral vertebræ on the left side and was completely overlooked when the abdomen was opened. Her twin sister was investigated and found to have a normal genito-urinary tract.

Thom (1928) collected from the literature 117 cases of partial urinary incontinence due to the uncontrolled drainage of an ectopic ureter which opened on to the vestibule in 45, into the urethra in 37, into the vagina in 32 and into the uterus in 3. The 2% to 3% of individuals with duplication of the ureter on one or both sides do not belong to this category unless one or more of the ureters has an extra-vesical outlet. 3 patients in this series had partial urinary incontinence from this cause.

(1) Two accessory ureters opened into the vaginal vault in addition to the two ureters that opened in normal position into the bladder.

(2) A left ureter opened into the vault of the left side of a double vagina. A single ureter, the right, opened into the bladder. Neither an intravenous pyelogram nor an aortogram revealed any evidence of the presence of a left kidney. Eventually exploration of the left loin exposed a hypoplastic left kidney which was removed with complete cure of the partial incontinence. Methylene-blue injected into the ureter came through to the left vaginal vault.

(3) A woman aged 60 years had had 6 children and was twenty years past the menopause. She had always dribbled urine since "her mother dropped her as a small child." She went to her doctor having noticed blood in her urine and a blood-stained discharge, but a full renal investigation and a uterine curettage were both negative. Hæmaturia continued, now having been present for five months. During a pelvic examination a bead of blood-stained urine was seen to exude from a small opening in the mid-line 1 cm. behind the external urinary meatus. Mr. G. C. Tresidder, one of our urologists at the London Hospital, removed a right kidney with two pelves; about the upper one-third of the kidney was largely replaced by a Grawitz tumour.

In conclusion, and to maintain a due sense of proportion, I would refer back to uterus and vagina simplex—the heritage of the vast majority of womankind. Thereby I would emphasize once again that the anomalies which I have discussed affect but a very small proportion of women.

I would like to thank my colleagues, past and present, for the use I have made of their cases.

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THE following cases and specimens were shown:

Imitation Patterns in Uterine Tumours.—Dr. HANS BETTINGER.

Uterine Chorion Epithelioma.—Dr. P. E. HUGHESDON and Mr. HERBERT REISS.

Four Cases of Mono-amniotic Twins.—Mr. ALISTAIR GUNN.

Giant Sections of Uterus.—Mr. ROBERT M. CORBET and Dr. A. A. MILLER.

Recurrence of Hydatidiform Mole, Presumed Second Mole, within Twelve Months.—Miss DOROTHY M. GRATTON.

Polycystic Disease of the Liver Presenting as a Gynæcological Problem.—Mr. MOSTYN P. EMBREY.

Primary Adenocarcinoma of the Vagina.—Miss JEAN MCFARLANE.

Post-abortal Tetanus.—Miss JEAN SHARPE.

Fibroid Causing Massive Ascites.—Mr. ANTHONY C. PEARSON.

BOOK REVIEWS

Techniques and Procedures of Anæsthesia. By John Adriani, M.D. 2nd edit. (Pp. xiv+568; illustrated. 66s.) Oxford: Blackwell Scientific Publications. 1956.

The title of this book accurately describes its contents which are presented in a didactic tabular form with numbered sentences, opposite which are brief explanatory phrases giving some of the physiological, pharmacological or practical reasons for the opinions expressed. This method of presenting the information makes it difficult to stress the relative values of the various points which are considered, and unfortunately these are seldom even enumerated in the order of their importance.

The reviewer finds himself out of sympathy with this approach in a volume of this magnitude, and feels that the omission of any discussion of basic physiological principles has resulted not only in much needless repetition but has also tended to impair the value of many of the—admittedly condensed—opinions presented.

It may seem churlish thus to criticize a work which has been reprinted six times, but as it is now offered in a greatly enlarged second edition this failure to stress the important points out of a mass of tabulated data becomes more noticeable, and may even be considered misleading to the point of being dangerous.

The section on succinyl-choline, for example, includes without any amplification other than that it is a disadvantage of the drug, the statement "In some individuals an apnœa may result (central depression)". It is not made clear that respiratory paralysis from peripheral neuro-muscular block is to be expected in every case, except perhaps when only extremely small doses are administered. On the other hand the section on controlled respiration makes no mention of the relaxant drugs which so facilitate this now commonplace procedure and obviate the necessity of giving large doses of drugs which depress the central nervous system. To the English anæsthetist the cursory mention given to the muscle relaxants and to controlled respiration is indeed surprising in an anæsthetic treatise published in 1956.

He will also feel, perhaps, that in the section on spinal analgesia the author lags behind contemporary thought in not stressing the importance of autoclaving all drugs and equipment used for this purpose. Again, in the section on rectal anæsthesia there are nine pages devoted to the obsolescent Avertin while a further page is given to trichlorethanol—a drug long abandoned in this country as too dangerous.

There are many other opinions expressed in these pages which invite comment, but the author in his introduction has disarmed the critic by pointing out the impossibility of assembling a book of techniques which would please every anæsthetist; as he rightly says the subject is not one to be learnt from a book.

Nevertheless, this volume contains much useful information; it will give the junior anæsthetist an idea of the wide scope of his specialty and of the many procedures he will have to study, and may also provide his teacher with some conveniently assembled data on which to base his lectures.

Atlas of Exfoliative Cytology. Supplement 1. By George Papanicolaou, M.D., Ph.D. (Illustrated; 32s.) London: Harvard University Press. Cumberlege. 1956.

The present supplement—the first to be issued—to Dr. Papanicolaou's Atlas of Exfoliative Cytology contains sixteen new coloured plates together with the appropriate letterpress. Most of the plates present three photomicrographs of each tumour—two of conventional histological sections at low and high power and one of cells from the same neoplasm as seen in exfoliative smears. Such comparisons are of great value to pathologists seeking to learn more about these newer diagnostic methods and to correlate the appearances in smears with those in paraffin sections with which they are more familiar.

In this supplement, four new plates each are devoted to the female genital and the respiratory systems, two each to the male genital and the digestive systems and the remainder to the breast and to various exudates. The technical production of these coloured plates is of a very high quality, and when used by pathologists who have mastered the author's staining techniques—as described in the main volume—the illustrations included in this supplement should prove of further help in accurate exfoliative cytological diagnosis.

Blood Transfusion in Clinical Medicine. By P. L. Mollison, M.D., M.R.C.P. 2nd edit. (Pp. xxv+587; illustrated. 45s.) Oxford: Blackwell Scientific Publications. 1956.

Dr. Mollison's monograph, now in its second edition, is, in the reviewer's opinion, without question the most complete and authoritative work on blood transfusion now available in English. It is particularly valuable because it is written by a man whose extensive and

perhaps unique practical and research experience in this field dates from the beginning of World War II and the discovery of the Rh blood groups, and it is a reminder of the astonishing progress that has been made in the understanding of the human blood groups and blood transfusion since that time.

As is right in a book which is primarily based on, and illustrated by, the author's own experience, Dr. Mollison does not confine himself strictly to the laboratory and clinical sides of blood transfusion; he enriches the text by including most valuable chapters and sections on subjects on the fringe of his main theme, such as blood volume, normal blood findings in infants, hæmolytic disease of the newborn, the use of ^{51}Cr-tagged cells in red-cell survival studies in disease and the use of ^{51}Cr in tracing the survival *in vivo* of red cells which have been exposed to isoantibodies.

The whole book is, in fact, packed full of up-to-date information on almost every possible facet of blood transfusion in theory and practice, and it includes three chapters of remarkable clarity, revised in collaboration with Miss Marie Cutbush, B.Sc., on the human blood groups. The bibliography at the end of the book now contains about 1,200 entries, and the inclusion of the titles to the references makes them particularly valuable.

This new edition, which is most meticulously produced, is 131 pages longer than the first edition published in 1951, but it is only 7s. 6d. more expensive. Every serious worker in the field of blood transfusion, whether physician, hæmatologist or clinical pathologist should possess a copy.

Principles of Chest X-Ray Diagnosis. By George Simon, M.D., F.F.R. (Pp. x+183; illustrated. 50s.) London: Butterworth & Co. (Publishers) Ltd. 1956.

The time is opportune and the need great for a re-statement of the principles underlying the interpretation of radiographs of the chest and no one is better qualified by his experience as a teacher to undertake this task than Dr. Simon whose present work fully justifies its title. It is essentially a teaching book in which the author happily excludes excessive clinical detail in order to concentrate on radiology. Radiographic technique in the form of "some hints" is brief and properly relegated to a terminal appendix, and anatomical considerations are confined to radiological landmarks and their variations. The interesting chapter classification is based on the characteristics of the particular radiological pattern, the shadows and translucencies being grouped according to their size, shape, distribution and outline and in each case the probable underlying pathological condition is indicated. This is a reversal of the normal textbook procedure of considering the radiological appearances under the heading of each of the various diseases in turn. Simon's method is, therefore, that of deductive interpretation, the daily system of the practical radiologist. He discusses most informatively the causes of common anatomical variations and explains some of the puzzling yet often normal features of lateral and oblique projections—for example, the high diaphragmatic cupola which simulates a pleural effusion. The chapter on mediastinal and diaphragm shadows is particularly helpful though the causes of diaphragmatic alterations could have been dealt with more fully. Simon demonstrates very clearly how difficulties in interpretation may arise from shadows cast by ribs or superficial tissues and how apparent "abnormalities" may be the result of even minor deviations from standard positions during radiography.

The use of the various radiological "indicators" is explained, particularly the diaphragm, the mediastinum, the lung fissures and the pulmonary vessels and there are strikingly instructive illustrations of segmental and lobar atelectases and consolidations. The author does not restrict himself to the classical appearances in each case but considers the modifications determined by pre-existing conditions, as instanced by the altered picture of middle lobe collapse when the main fissure is tethered.

Perhaps the sections which are likely to have most appeal because of their great practical value are those dealing with the classification of homogeneous shadows or discussing the nature of linear, ring and large circular opacities and there is an impressive list, which must be almost exhaustive, of the possible causes of disseminated, small, circular or reticular shadows. Bronchography and tomography are somewhat briefly dealt with although their uses and indications are clearly described. Readers would have been grateful for discussion of those shadows which constantly give rise to difficulty in tomographic interpretation. The large format has made it possible to include illustrations of a size adequate to demonstrate the points described in the text and the chapter and section headings in large clear type facilitate reference.

There are no major defects in this excellent book.

A minor fault is the author's use of terms that are either not in general use or have been discredited but in fairness to the reader he does define his own terms in the introductory chapter. The author's clear descriptive writing and his skilful use of magnificent illustrations and textual tables make this work, in the reviewer's opinion, easily the best teaching manual on chest radiology.

Anatomical Techniques. By D. H. Tompsett, B.Sc., Ph.D. (Pp. xvi+240; illustrated. 35s.) Edinburgh and London: E. & S. Livingstone Ltd. 1956.

This book is written primarily as a guide to part-time workers and prosectors who require some ready available information on the preparation of museum specimens of human anatomy. On the technique of dissection, much of what Dr. Tompsett has written has been known since dissections were first undertaken many centuries ago. Nevertheless it is useful to have this information available in print. On the mounting of anatomical material in Perspex containers there is much useful information and the detailed instruction given on the preparation of casts in synthetic resins makes a real contribution to anatomical techniques. Although some of these techniques are very highly specialized, many of the others are becoming a necessity for the proper understanding of the anatomy of such organs as the lung. Dr. Tompsett was one of the first persons to appreciate the possibilities of the synthetic resins in place of woods, metal and plaster of Paris which were formerly used.

The chapter dealing with the principles of anatomical illustration leaves much to be desired, but presumably this is not the author's field. In Fig. 26, which is taken as a prototype, the pointers are arranged in such a way that many of them run parallel to each other so that they look like railway lines. Interrupted lines are always preferable to continuous ones, as they do not cut up the illustration so much. This figure would have been much better reproduced as a simple "cut out" with the lettering arranged independent of the half-tone screen. In spite of this criticism the book can be recommended without reservation. It is well produced and is a credit to the publishers, E. & S. Livingstone Ltd.

Management in Obstetrics. By Andrew M. Claye, M.D., F.R.C.S., F.R.C.O.G. 2nd edit. (Pp. x+218; illustrated. 18s.) London, New York, Toronto: Oxford University Press. 1956.

This is a second edition of a book, first published in 1948, which has gained well-deserved popularity. It is not a textbook, but rather a series of essays covering the range of practical obstetrics. This second edition has grown in size, and the number of illustrations has increased. The text has been thoroughly revised and the references brought up to date.

This book is chiefly intended for the general practitioner obstetrician to whom it can be warmly commended on account of the lucidity of its style and the emphasis always on the practical. It is useful, either as reading matter or as a work of reference. The quotations which head many of the chapters are often delightfully apt and reveal the author not only as an obstetrician but one with a profound knowledge of English literature.

The new edition of this useful book will prove a contribution to the further raising of standards of midwifery and it will be of value, not only to the general practitioner for whom it is mainly intended, but also to all who practise the art of midwifery.

Neoplasms of the Domesticated Mammals. A Review. Review Series No. 4 of the Commonwealth Bureau of Animal Health. By E. Cotchin, M.R.C.V.S. (Pp. xv + 100. 20s.) Farnham Royal, Bucks.: Commonwealth Agricultural Bureaux. 1956.

This monograph, as the author states in the introduction, is a survey of the incidence of tumours in domesticated mammals, and is not a histopathological treatise.

No one is better qualified, in view of his extensive study of animal neoplasms, than Mr. Cotchin to undertake this detailed comparative survey. The omission, however, of any histological description of the neoplasms does not in any way detract from the usefulness of this handbook. It is something more than a critical review since it compares the tumour incidence in different animal species with that of man, and therefore contains information of interest to both the clinician and laboratory worker who are interested in the cancer problem.

The author begins with an admirable introduction extending over eight pages, which deals not only with the statistical study of tumour incidence, but also the mechanism of the spread of cancer in different animals. Apparently in some species metastases may occur by different routes than in man. In the subsequent chapters the author brings to light some interesting facts: the cat, for instance, would seem to be the most useful species in which to study carcinoma of the œsophagus, since it is the only domesticated mammal apart from man in which spontaneous cancer of that organ frequently develops. Methods are also discussed by which neoplasia can be experimentally produced in the organs of some species; information which is of direct interest to those engaged in tumour induction. Furthermore, we learn that melanotic tumours in the cat are very rare, whilst they occur often in both the dog and the grey horse. Also, we find that neoplasms of the mammary gland are particularly frequent in the bitch but are chiefly of the benign type, whilst although they occur less frequently in the cat they are invariably present in the malignant form. Carcinoma of the stomach and gall-bladder, both of which are common in man, are

apparently rarely met with in domesticated mammals and, when they do occur, they are diffuse or hyperplastic rather than neoplastic. It is curious to find that carcinoma of the prostate, which is frequently seen in man, is very rare even amongst the higher mammals; but, on the other hand, testicular tumours are particularly frequent, especially in both the dog and horse.

These comparative studies are not only of interest, but are of importance, when dealing with the ætiology of cancer, since any explanation for their rarity in some animals might help to explain the cause of a particular neoplasm common in man.

As a work of reference this monograph is well constructed with clear headings to the numerous sub-sections of each chapter. There is also an excellent bibliography of nearly a thousand references, all of which have been read by the author.

The Collected Papers of Paul Ehrlich. In four volumes. Volume 1—Histology, Biochemistry and Pathology. Edited by F. Himmelweit, M.D., Ph.D., F.R.C.P.Ed. (Pp. viii + 653; illustrated. Volume 1—£12.) London and New York: Pergamon Press. 1956.

This work may, without exaggeration, be described as one of the most ambitious and important contributions made to medical literature and medical history this century, and doctors, scientists, historians, and librarians owe an enormous debt of gratitude to the editor, Dr. Himmelweit, to the late Martha Marquardt, to Sir Henry Dale, to the Pergamon Press, and to the Wellcome Trust for the part they have played in translating what might well have remained a pious dream into the realm of reality. The first volume contains a scholarly and enlightening introduction by Sir Henry Dale and 55 of Ehrlich's papers which are arranged in the following sections: Practice and theory of staining in histology; Cytology of the blood in health and disease; Staining of bacteria and its application to diagnosis; "The requirement of the organism for oxygen" and allied biochemical studies; Pharmacology, therapeutics, and toxicology; The diazobenzenesulphonic acid and dimethylaminobenzaldehyde reactions. The earliest paper is dated 1877 and the last 1904. The great majority of the articles are in German. Two previously unpublished ones are also translated into English: Ehrlich's inaugural dissertation (Leipzig, 1878), entitled "Contributions to the theory and practice of histological staining", and his *Habilitationsschrift* (thesis for recognition as university teacher), "The requirement of the organism for oxygen: an analytical study with the aid of dyes" (1885). There are five coloured plates and a frontispiece showing Ehrlich aged about 40.

Having enjoyed the literary feast provided by this unique and fascinating volume, it may be greedy and ungrateful to ask for more, but to the reviewer it seems a great pity that a few lines of comment did not accompany each article, explaining its historical significance and its value to-day.

The price per set is £28. Volumes 1, 2, and 3 can be bought separately for £12 each; the final volume which will contain a complete bibliography, will not be sold separately, but will be available with any other volume at £5.

Pathological Histology. By Robertson F. Ogilvie, M.D., D.Sc., F.R.C.P.Ed., F.R.S.E. Foreword by A. Murray Drennan, M.D., F.R.C.P.Ed., F.R.S.E. 5th edition. (Pp. xi + 482; illustrated. 52s. 6d.) Edinburgh and London: E. & S. Livingstone Ltd. 1957.

The fact that this book has been re-issued seven times since its first appearance in 1940 attests the appreciation that has been accorded to it by large numbers of the medical students for whose training in morbid histology it was originally prepared. The present edition has been further enlarged, and the author hopes that this expansion will render the volume of greater value to more advanced readers.

The general standard of the coloured illustrations, of which there are more than three hundred, is satisfactory, though in spite of the weeding that has taken place in successive editions, a number could still be bettered. Most of them are made from the hæmatoxylin and eosin stained sections with which students are generally familiar, though other methods are used when needed for the display of particular structures. The book can therefore be employed usefully as a bench manual in morbid histology classes, though, as Professor Drennan remarks in his foreword, "No book on morbid histology can ever replace study of the actual specimen, but a book may so vividly represent and interpret the original that its study is greatly facilitated and revision of knowledge simplified."

Whether or not with the increasing competition for time in the curriculum, the student's limited period of study in a pathology department is most profitably spent in such a detailed examination of this branch of morbid histology is a matter which each teacher must decide for himself. In the reviewer's opinion there are other aspects of pathology, functional and biochemical, that nowadays are equally, if not more, rewarding.

Section of Psychiatry

President—WILLIAM SARGANT, M.A., F.R.C.P., D.P.M.

[*November* 13, 1956]

DISCUSSION ON THE TREATMENT OF MORBID ANXIETY [*Abridged*]

Dr. E. A. Bennet: *Psychotherapy*

The treatment of the morbidly anxious patient, by psychotherapy, should be confined to those who are emotionally and intellectually capable of co-operation, and a patient should not be accepted for treatment unless the diagnosis has been made on affirmative grounds, that is from the presence of the known characteristics of the state of disturbing and irresolute suspense which we describe as morbid anxiety. In making a diagnosis we aim at probabilities, approximations, rather than certainties; and the diagnosis may well be altered as we observe our patient. But this does not permit us to commence treatment on the basis of an ambiguous diagnosis or a negative diagnosis which infers psychological illness from the absence of organic disease. Whatever its form and whether combined with physical methods of treatment or not, psychotherapy is a co-operative procedure in which one person seeks to influence the health of another. It is essentially the interaction of two personalities. Jung (1933) puts the matter concisely: "By no device can the treatment be anything but the product of the mutual influence in which the whole being"—that is the personality, containing both conscious and unconscious elements—"of the doctor as well as that of the patient plays its part."

The relation of doctor and patient on a consciously harmonious level, as in our association with acquaintances, is described as "rapport". But when the unconscious of either doctor or patient is clearly involved, "transference" is a better term. Transference occurs whenever psychotherapy goes beyond the superficial level, and as it is a phenomenon of projection we cannot know to what extent the therapist and the patient will be involved. The interaction of the personality of the doctor and that of the patient means more than medical empathy, that is the doctor's ability to value the feelings of his patient, for the patient's valuation of the doctor's feelings also plays a part. The therapist will try to understand his patient and he must expect the patient to return the compliment. We encourage our patients to be natural, to drop pretences, knowing that the inner will affect the outer anyhow, and we should do the same. There is a danger that the analyst who has difficulty in making personal relations within or without the analytical sessions, may unknowingly protect himself behind the patient's manifestations of transference, denying his own part in the proceedings, although his projections, like those of his patient, are active ingredients. Successful psychotherapy is a joint effort, the product of the whole influence of each personality. While it is unreal to believe that every contact between therapist and patient is or should be within the transference situation (for rapport also provides possibilities of treatment), it is equally unreal for the therapist to regard transference as an abstraction with which he is not concerned. Whether he concerns himself with it or not, it will still be there, playing its part. My own opinion is that transference is of central importance, but that it is a mistake to make it the main focus of attention; nor need it always be analysed. It is a medium of contact, for good or ill, in which the

unconscious of the patient and that of the doctor can evolve and develop. Often the unspoken is more valuable than the spoken word.

The division of the neuroses into hysteria, anxiety and obsessional states, though deceptively simple, has one thing in its favour: it helps us to see that the energy, the drive behind psychoneurotic and similar symptoms, is differently directed, achieves its purpose in different ways. The attitudes, that is the activities represented in symptoms of neurosis, call for something more than an ætiology framed solely on a simple developmental or cause and effect plan. In addition we should observe the attitude of the patient towards the movement of life, the passage of time. Bearing this in mind, I should place hysteria at one end of a scale and obsessional states at the other, with anxiety-states occupying an intermediate position. The patient with hysteria meets the present as if it were the past. In a fugue, for example, the dissociated individual wanders, not aimlessly but purposively, seeking to return to a place where once upon a time life was almost problemless; and should the morbid anxiety undergo conversion we have an attitude of dependence, even of childishness. It is this application of past notions to present problems which makes hysteria so resistant to treatment. On the other hand, the obsessional patient, who is always morbidly anxious, meets the present as though it were the future. The patient with the typical symptoms of an anxiety state falls between these two, for he is rooted in the present and cannot see either the past or the future in its true perspective. The relevance of these observations to the treatment of morbid anxiety will be illustrated if we consider some features in the group of patients with obsessional symptoms.

Three characteristics, usually found in combination, call for special attention in the treatment of obsessional patients: these are (1) a conscious sense of guilt; (2) secrecy regarding the symptoms—the obsessional neurosis is the secret neurosis; and (3) what for lack of a better term I call the time element.

(1) The patient with a compulsion to pursue repetitive actions or thoughts feels guilty and oppressed because of the content of his symptoms, which nevertheless fascinate him. Consciously he loathes his acts or thoughts, yet their interest-value compels him to cling to them, and at the same time the conscious sense of guilt permits him to feel exonerated from the burden of responsibility for them. In consequence he has an insoluble problem: his conscious sense of guilt imparts a feeling of righteousness because of the condemnation of his compulsions, thus enabling him at the same time to own and yet to disown the satisfaction which his interest provides. The creation of an insoluble problem, such as this, is indeed one of the characteristics of the obsessional neurosis.

(2) The existence of the neurosis is a closely guarded secret and insulates him from others. But the secretiveness has its value, for like the guilt it preserves the symptoms, and close friends or relatives may be unaware that the patient has any symptoms, let alone their nature.

(3) Morbid anxiety in the obsessional patient is anxiety about the future on which his eyes are fixed almost to the exclusion of the present. His symptoms are an attempt to influence the future by magical thinking. Filled with morbid expectation he is deeply concerned with the passage of time. A patient of mine had a phobia concerning clocks and particularly clocks which struck the hour: "Time runs, the clock will strike." The striking of the clock sounded a note of inevitability—the time had come for something to happen. "Time, the subtle thief of youth" provides the insoluble problem of the obsessional, for all obsessional rituals aim at making time stand still. Behind the neurosis lies a morbid fear of the future and with it the thought of death. Thus the obsessional with a show of efficiency over current affairs (which deceives himself and others) is surprisingly ineffective. Intellectually he is often gifted but, being all for delay, he falls short of the goal which his attainments warrant. In him we see the hidden wish that "time may cease and midnight never come". More than any other, the obsessional patient is hurt and hindered by morbid anxiety and I suggest that the consideration of these three characteristics —the sense of guilt, secrecy and the time element—give an insight into his mind which is invaluable in treatment. It is difficult to understand how anyone can treat an obsessional neurosis, or any neurosis, purely by a reductive technique.

When it is possible—and often it is—to help a patient (obsessional or otherwise) to see the state of affairs behind the morbid anxiety with which his symptoms are clouded, then he has taken the first step towards being a more effective and much less anxious individual. He acquires a respect for his mind, conscious and unconscious, in its personal and impersonal aspects. To achieve this enlargement of consciousness we give the chief place in the treatment of morbid anxiety to dream analysis and to the use of drawings and paintings to amplify the dreams and particularly their symbolic content, as well as the product of active imagination. The patient is thus in the treatment, sharing the work with the

therapist. Consequently the interviews can be spaced out, often being weeks apart, till the patient, no longer bound by morbid anxiety, takes over responsibility for himself.

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Dr. H. J. Shorvon: The appreciation of the physiological basis of anxiety, as well as the psychological, and the viewpoint that much morbid anxiety is the result of conditioning, has led to the approach whose aim is the disrupting of conditioned patterns of anxiety by chemical or other means.

Before and during the First World War there were only psychotherapy, hypnosis, bromides, paraldehyde and opiates. Barbiturates were not used before 1930. Sodium amytal in 1930 and Seconal in 1935 were the first of the barbiturates to come on to the market. Drug abreaction techniques were developed during the last war, first with intravenous barbiturates in 1940, and then under open ether by Palmer in North Africa and later by Sargant and myself at the time of the Normandy campaign. Modified insulin for sedative and nutritional purposes was first used on a large scale by Sargant at the time of Dunkirk. In 1944 Rogerson introduced the inhalation of nitrous oxide for abreactive and psychotherapeutic purposes, and in 1948 Meduna began his passive treatment of anxiety states by the repeated inhalations of a 30% carbon dioxide mixture. Sargant introduced intravenous Methedrine as an abreactive agent in 1948, and López-Ibor in Spain in 1950 found intravenous acetylcholine of value in certain types of tension. In 1950 Hirschfeld and Alexander in America tried subconvulsive electrical stimulation for the treatment of tension states, and this therapy was established in this country soon after by Spencer Paterson. Also since the war, the antihistaminic drugs such as Phenergan have developed and played an important part in treatment. In the past few years many "tranquillizers" have appeared on the market. The word is meant to indicate a drug which will ease anxiety and psychomotor agitation without affecting consciousness to any extent.

The personality of the patient, the intensity of his symptoms and whether his morbid anxiety is a manifestation of an anxiety state or secondary to some other disorder, such as melancholia, an obsessional state, &c., must be assessed before the value of the particular tranquillizer can be judged.

Some random observations on the use of these drugs may not come amiss. Bromides may be very useful in easing severe tension, but are apt to aggravate depression, and should be avoided in the aged, especially where renal function is impaired. I have recently seen two cases of addiction and repeated overdosage with Persomnia tablets, which unfortunately can be bought over the counter. They showed tremors, acneiform eruptions, ataxia, and spells of confusion with paranoid ideas and hallucinations.

The short-acting barbiturates have no superior in easing morbid anxiety. Addiction is rare although habit formation is commoner, and patients usually cut down the prescribed dose on their own initiative. Unfortunately, excessive dosage over a prolonged period may engender or exacerbate anxiety instead of relieving it. Seconal, ¾ grain, and sodium amytal, 1 grain, are the most effective drugs for immediate relief of acute panic or fear. The use of barbiturates in continuous narcosis is well known, but care must be taken in their withdrawal, particularly in obsessional personalities who may even show schizophrenic-like symptoms for a few days. I rarely use long-acting barbiturates such as phenobarbitone in the treatment of anxiety, because of depressant effects.

Antihistaminic drugs such as Phenergan are useful, particularly with patients in bed who tolerate 150–300 mg. daily, and I have also found the drugs of value in the relief of tension in sufferers from generalized pruritus and other psychosomatic disorders. They combine well with chlorpromazine in controlling agitation and restlessness.

Chlorpromazine or Largactil, the first of the tranquillizers, has been tried extensively since 1952. Most ambulant patients dislike it as they often feel tired and derive little easing of tension. Linford Rees and Lambert did, however, find that 50% of 150 patients showed considerable clinical improvement although two-thirds relapsed within a few weeks despite continued medication. Jaundice is an important complication, usually occurring within the first ten days of taking small doses. The drug, however, is very useful in in-patient treatment of acute anxiety reactions and for acute psychotic illnesses such as manic or schizophrenic excitement if given in bigger doses of 50–100 mg. three times a day,

or more.. It combines well with barbiturates in continuous narcosis, and is useful in combating a post-E.C.T. flare-up of tension or damping down the anxiety of the agitated melancholic. A feature is its tendency to increase appetite, and gratifying results are often obtained when combined with modified insulin.

Mephazine or Pacatal is chemically related to chlorpromazine and is said to have fewer side effects apart from dryness of mouth and blurring of vision. I have found it useful in easing tension of patients suffering from involutional depression who are not responding to E.C.T.

Reserpine or Serpasil, a rauwolfia alkaloid, can be regarded as still on trial. It is mildly hypotensive, and useful in patients suffering from hypertension with anxiety. In large doses of 8–10 mg. daily it can control the motor over-activity and aggressiveness of manic and schizophrenic excitements. Toxic side effects, Parkinsonism and œdema are not uncommon complications. Depression is a serious risk in patients on large doses. I use it very little in out-patients because of the unpleasant side-effects of tiredness, congestion of nose, diarrhœa and depression, but, like chlorpromazine, it tends to increase appetite and has been useful in conjunction with modified insulin in treating anorexia nervosa.

More recent tranquillizers, part of the feverish search for a panacea for anxiety, include benactyzine compounds (Suavitil, Nutinal, and Covatin), the meprobamates (Equanil, Miltown, and Mepavlon) and hydroxyzine compounds such as Atarax. Little is known of their pharmacological or possible harmful effects. Suavitil has received enthusiastic notice in Scandinavian papers by Jacobsen, Munkvad, &c., and in the *British Medical Journal* by Davies. It is said to produce a barrier between the patient and his problems. Lieberman and Vaughan in a recent paper consider this drug the best of the newer tranquillizers in the treatment of diffuse non-specific anxiety and tension. I have not found this to be the case with the majority of my out-patients on this drug, and indeed most anxiety patients asked to be taken off it. I used a total of 3 mg. daily. At St. Thomas's Hospital, da Fonseca and West carried out a trial of benactyzine and found it useful in anxiety reactions due to environmental stress and panic attacks in obsessive personalities. They, too, were disappointed with the overall results.

Perhaps the most widely used new tranquillizer is meprobamate, despite its cost. According to West and da Fonseca, Miltown has become the fourth most commonly prescribed drug in America and there is no doubt that Equanil, the same drug in England, is greatly in demand. The chemical formula is closely related to mephenesin, and in doses of 400 mg. (one tablet) three times a day it has been hailed in the U.S.A. as *the* drug for reducing morbid tension and anxiety because of its muscle relaxant and sedative effects. It is also said to be a fifth as toxic as barbiturates and not liable to create addiction. West and da Fonseca in the Psychiatric Department of St. Thomas's carried out three separate controlled trials. They found that 58% of patients classified as anxious and tense were helped. The results were not so good as those claimed by American workers. The relief was in the subjective sphere rather than in overt somatic manifestations of anxiety. Meprobamate was also compared with sodium amytal in a further series but no marked differences were found in effectiveness between these two drugs. However, clinically, meprobamate often seems more useful than a barbiturate when irritability is a marked feature. No serious side effects were observed. It therefore appears that Equanil has the beneficial effects of barbiturates, but with less risk of toxic complications and addiction. Although I have not carried out statistical trials, I have used meprobamate on a large scale in a variety of psychiatric syndromes and found it a useful drug in the out-patient treatment of anxiety states, particularly phobic states, fears of insomnia, and other mono-symptomatic fears. I have often seen the drug slow down feelings of impatience and frustration, but it also increased dullness in the morning and depression. It is best avoided where a depressive element is present in the illness. It also appears to reinforce the effect of barbiturates, and is therefore useful when added to such hypnotics at night, in order to reduce the total barbiturate consumption and to facilitate sleep.

A combination of stimulant and sedative drugs, for instance, Drinamyl, is particularly helpful in phobic anxiety states in an obsessional setting. The obsessional patient feels at his best when cortically stimulated, yet soothed at the same time. The result is activity in a relaxed and optimistic mood.

López-Ibor in 1950 introduced repeated intravenous acetylcholine injections in the treatment of tension states. Sargant, Phillips and Hutchinson found it useful with patients of good personality suffering from phobic tension states, particularly in driving personalities who carried on their work despite periods of debility. Hawkings

and Tibbetts have questioned these results, but their clinical material does not appear to correspond.

Abreactive techniques were fully discussed in papers in the R.S.M. in 1950 and 1953. Intravenous barbiturates were first used at the time of Dunkirk, and the excitatory abreaction of traumatic experiences in people of reasonably good previous personalities facilitated an emotional release, and often prevented the implantation of recently acquired neurotic patterns of behaviour. Soldiers in a state of acute fear and showing tics and violent movements of all kinds, in addition to hysterical inhibitory phenomena such as amnesia, aphonia and paralysis, felt "a load off their minds" after effective abreaction. It was usually necessary to follow this up with adequate sedation for some days, if the patient was to emerge into, and remain in, a state of mental equilibrium. This approach is, of course, equally useful in the treatment of anxiety states following traumatic episodes in civilian life. It was found later in the war that in untreated or inadequately treated cases, the neurotic reactions had become firmly established as a result of anxious rumination over unrelieved traumatic incidents.

Intravenous barbiturates failed to reactivate the affect attached to those experiences, and a dull recital of facts ensued, without benefit to the patient. During the Normandy campaign ether inhalation on an open ether mask was found to produce stronger excitatory abreactions in the acute psychiatric battle casualties than the barbiturates, with a correspondingly greater relief of anxiety and tension. Similar difficulties with the intravenous barbiturates were again experienced in more chronic cases, but the occasional ether abreaction still may be a useful procedure from time to time in the treatment of chronic anxiety states where traumatic incidents have played an obvious part in the precipitation of symptoms. The most difficult patients to treat, the anxious obsessionals, may be helped by intravenous Methedrine in small doses of about 15 to 20 mg., used either as a psycho-therapeutic aid or for encouraging abreaction. The drug relaxes the patient and reduces inhibition by cortical stimulation, so that everything is discussed with a feeling of confidence in extra-clear consciousness. Barriers are rapidly broken down, much repressed material is brought to the surface, and a good deal of tension is released over a period of time.

I also find that psychotherapy with the aid of intravenous Methedrine, and the occasional use of ether abreaction where there is some resistance to be overcome, or traumatic incidents to be discussed, is one of the best ways of treating phobic anxiety states with panic attacks, and psychosomatic disorders, such as skin disturbances resulting from emotional factors.

The pharmacological and clinical actions of the older drugs, bromides and barbiturates, have now been fairly well worked out, but few controlled studies have yet been carried out with the host of new tranquillizers. Little is known therefore about their mode of action and the indications for their use. Some may prove useful, and I suspect the majority will be discarded in time as the evidence about their value is slight.

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Section of Otology

President—PHILIP J. JORY, D.S.O., F.R.C.S.

[*November* 2, 1956]

Mr. PHILIP J. JORY delivered his Presidential Address entitled **Random Reminiscences.**

[*December* 7, 1956]

DISCUSSION ON NOISE AND ITS EFFECTS

Dr. J. D. Hood (Otological Research Unit, Medical Research Council, National Hospital, Queen Square, London):

Measurement of Noise

Noise may cause physical damage to the organ of hearing. It may interfere with communication. When unwelcome, it may give rise to mental irritation, and from this is derived what is perhaps its best-known definition, namely, that noise is any unwanted sound.

All of these ill-effects are related to certain of its physical attributes, in particular intensity and frequency. These can be measured, and it is the aim of this communication to outline firstly the technique of such measurements and, secondly, to relate their results to the frequency and intensity characteristics of the hearing mechanism itself.

Noise can be transient, periodic or aperiodic. In general, transient sounds consist of short duration changes of pressure; periodic sounds are those which can be shown to be repetitive over a certain period known as the fundamental period, and aperiodic sounds are those which show no particular period of recurrence. Sound intensity is measured by means of a calibrated instrument consisting essentially of a microphone, an amplifier and an indicating meter.

Table I affords some illustration of the intensity range with which we have to deal. If the normal threshold of hearing at 1,000 c/s be taken as the basis of our measurements, it will be seen that the noise level of a quiet office has a relative figure of 1,000, a busy street of 1,000,000, and thunder almost a billion. To accommodate this enormous range of intensities it is convenient to convert the relative intensities into decibels.

The relationships are apparent from Table I. A tenfold increase in sound energy corresponds to 10 db., a 100-fold to 20 db., 1,000-fold to 30 db. and so on.

TABLE I

	Relative intensity	Intensity in db. re 10^{-16} watts per sq. cm.
Threshold of hearing at 1,000 c/s 10^{-16} watts per sq. cm.	1	0
Quiet garden	100	20
Quiet office	1,000	30
Average office	10,000	40
Vacuum cleaner	100,000	50
Busy street	1,000,000	60
Motor vehicle	10,000,000	70
Heavy street traffic	100,000,000	80
Underground railway	1,000,000,000	90
Boiler shop	10,000,000,000	100
Thunder	100,000,000,000	110

Measurements of this kind, however, have only a limited value, since they afford no information in respect of the frequency distribution of the noise. This is of particular importance, for example, in investigations of the masking effect of noise upon speech communication. Alternatively, a precise knowledge of the spectral composition of the noise of a machine may lead readily to the location and suppression of the noise from the offending components. For this purpose it is usual to subject the noise to some form of frequency analysis, provided the noise spectrum remains reasonably constant over a period of time.

The noise is picked up by a microphone, amplified and passed in turn through a number of filter circuits which break up the noise into a number of contiguous bands of frequency of from 5 to 100 cycles. The energy in each band can be measured on a meter or displayed upon a cathode ray oscilloscope.

The choice of the band width is determined by the amount of detailed information required. In certain noises, for example, a few intense components are present in a very narrow band of frequencies. A wide band analyser would indicate only the average energy over the band, and thus the selective nature of the component would be undetected. The narrower the band width, however, the more stringent are the requirements of the filters and, of course, the more tedious and time-consuming the complete analysis.

In the majority of problems a detailed analysis is unnecessary, and it is usual to use filters which break the spectrum, not into equal frequency bands, but into octave or 1/3 octave bands. In this way, the whole spectrum can be covered with as few as 8 octave band filters, and such analysis has now become common practice.

Typical octave band analyses of the noise in an average office, a living room with the windows open, and the Underground Railway are shown in Fig. 1. In general, however,

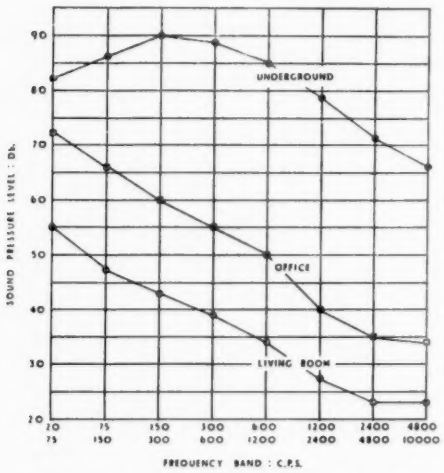


FIG. 1.—Octave band analysis of noise in (*a*) the Underground, (*b*) an office, (*c*) a living room. Adapted from the Handbook of Acoustic Noise Control, Vol. 1, Physical Acoustics, Wright Air Development Center Technical Report 52-204, with the permission of the Editors.

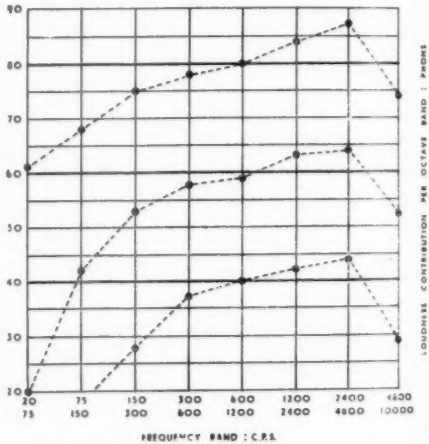


FIG. 2.—Computed loudness levels expressed in phons of noises with equal energy per octave at sound pressure levels of 40, 60 and 80 db.

we are interested in the loudness contribution each band makes to the overall noise level, and this information is not immediately apparent from such an analysis. This is exemplified in Fig. 2 which shows, by way of illustration, three flat curves drawn empirically at different intensity levels. The approximate loudness contribution in phons of each octave band is shown by the three interrupted curves.

The phon is a loudness unit defined in terms of the equivalent loudness of a 1,000 cycle tone. It enables the loudness of any pure tone or of any complex noise to be expressed in subjective units. The three loudness curves have been computed on this basis. Their dissimilarity to the intensity curves exemplifies the marked divergence between the subjective and objective attributes of noise. This is due to the fact that loudness is a non-linear function of both frequency and intensity, relationships which are illustrated in the well-known equal loudness contours shown in Fig. 3.

These were established by Fletcher and Munson (1933), and have for many years been the basis of most present-day psycho-physical computations. They differ, however, in certain respects from the more recent and comprehensive data of Dadson and Robinson at the National Physical Laboratory (1956).

The lowest curve is the threshold of hearing, while the upper curves express the intensities of tones at all frequencies which evoke equality of loudness with a tone of 1,000 cycles at the levels shown. These are, by definition, the loudness levels in phons.

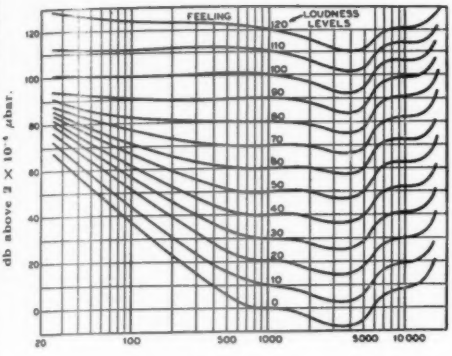


FIG. 3.—Sensitivity curves of the human ear (Fletcher-Munson).

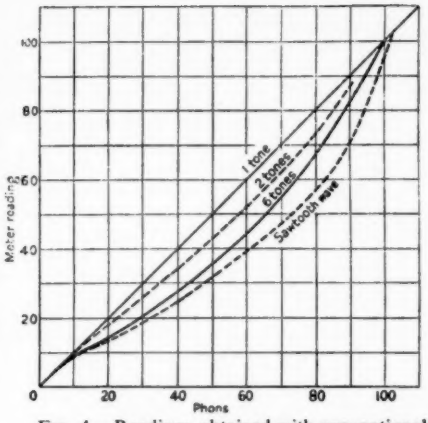


FIG. 4.—Readings obtained with conventional objective noise-meter, showing increase in error with number of components in noise. Reproduced by permission of the Editor of the *Journal of the Institution of Electrical Engineers* (Churcher and King, 1937).

The phon is a convenient unit because it provides us with a subjective scale which can be extended to any noise, however complex. Thus, the loudness level of a noise in phons may be determined by adjusting the intensity of a 1,000 cycle tone until it appears equal in loudness to the noise. The intensity of the 1,000 cycle tone in db. above the reference level 10^{-16} watts per sq. cm. is the loudness level of the noise in phons.

This procedure has obvious disadvantages. It is difficult and time-consuming. The observer must have "normal" hearing at all frequencies, and experience has shown that no two observers are likely to be in complete agreement. For these reasons, an obvious need has arisen for an instrument capable of providing objective measurements which match the subjective response of the perfect observer. Although a few highly specialized instruments have been developed, most commercial so-called sound level meters fall far short of this ideal. They can, however, provide useful measurements provided due regard is paid to their limitations and these will be considered as follows:

Let us suppose the sound level meter to be so designed that its frequency response followed the threshold sensitivity curve of the ear and further that with this instrument we now wish to record the loudness level of a 100 cycle tone 40 db. above threshold.

It will be seen from Fig. 3 that such a tone will have a loudness level of 70 phons, and this is far removed from the 40 db. it would in fact register. The reason for this is that at 100 cycles, loudness increases more rapidly with intensity than at 1,000 cycles. Such discrepancies would occur at all frequencies with the sole exception of 1,000 cycles which, by definition, would be a true reading in phons. The ideal sound level meter should be able to match the loudness function of the ear at all frequencies. Since this presents insuperable difficulties in design and construction, it has been the practice both here and in America to adopt a compromise. Frequency weighting networks are incorporated, by which the overall frequency characteristics may be adjusted to agree approximately with these equal loudness curves at certain chosen levels, usually 40, 70 and 100 db. If the level of the sound lies within the range 20 to 55 db., then the 40 db. network will be selected; 55 to 85 the 70 db. network, and 85 to 140 the 100 db. network.

If the sound to be measured is a single pure tone, the readings of the meter will provide a good approximation the noise level in phons. When, however, the sound to be measured is a complex one, as is usually the case, we are faced with a further serious difficulty.

If two or more tones are present, the conventional sound level meter will indicate the R.M.S. sum of their equivalent 1,000 cycle pressures. For example, if two tones of the same phon level are presented to the meter, the total sound intensity will be doubled, and its reading will be 3 db. higher than that which would be obtained if they were presented separately. Unfortunately, the ear does not sum loudness in this simple fashion. Two tones of moderate intensity and of equivalent loudness, separated by an octave in frequency, sound approximately 10 phons greater than the separate loudness of each. As the number of

tones increases this discrepancy increases, and for a multitone noise may be as much as 25 phons.

This effect is strikingly illustrated in Fig. 4 from a paper by Churcher and King (1937). This shows sound level meter readings for four different noises. One a single pure tone, one of two tones each of equivalent loudness, one of six pure tones each of equivalent loudness, and a saw-tooth wave. The loudness values in phons of each of these sounds have been computed, and are plotted along the abscissa. It will be seen that the departures of the meter readings from the true values are greatest at moderate intensities, and that as the number of components increases the inaccuracy of the instrument increases.

What then are the uses of an instrument which is capable of providing such fallacious readings? As long as due regard is paid to the fundamental defects described, and the results interpreted accordingly, they can provide valuable information, particularly in problems involving comparative measurements at different levels of either the same noise, or of noises of similar frequency spectra. A memorandum on the use of sound level meters compiled by the British Standards Institution (1948) stresses two points: firstly, that the noises to be compared must be substantially of the same composition, and secondly that the resulting measurements can validly only be expressed in sound level readings in decibels and not in phons.

The following investigation of the variation of voice level in the presence of noise of varying intensity will serve as a somewhat elementary example of the use of a sound level meter.

The experimental set-up is shown in Fig. 5.

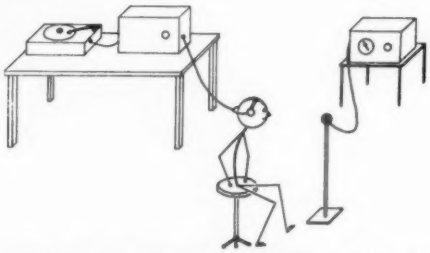


FIG. 5.—Experimental set-up for investigating variations of voice level in the presence of noise.

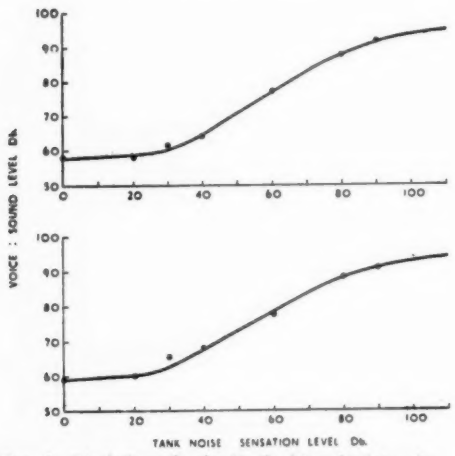


FIG. 6.—Variation of voice level with noise intensity.

The subject, a young adult with *normal hearing*, wears a pair of headphones connected by way of an attenuator calibrated in decibels to an amplifier and a gramophone pick-up. A record of a tank noise was used, and by varying the attenuator the subject's threshold to this

noise was first determined. The subject was asked to repeat six chosen words, and their level was recorded with a Western Electric sound level meter, the microphone of which was placed 3 ft. away from the speaker's mouth. The first measurements were made in the absence of any noise, and these were followed by a further series of measurements in which the level of the tank noise was raised in steps of 10 db. above the subject's threshold. Typical results from two of six similar subjects are shown in Fig. 6.

One of the most striking features revealed by these investigations was that in all six subjects, apart from some slight variation in level, the curves followed the same general course. As will be seen, the effect of noise upon voice level begins at the surprisingly low sensation level of 20 db. Thereafter, voice level increases linearly with noise until a maximum is reached at a noise sensation level of 90 db., at which point the voice appears to have reached the limit of its ability to match the noise.

Not the least surprising of our findings was the fact that, for any given noise level, the subjects were able, without any conscious effort, to maintain the level of their voices with great constancy, yet attempts to reproduce and to maintain the higher voice levels after the noise had been removed required very considerable conscious effort. It would seem that voice level is rigidly controlled by some central reflex mechanism analogous to the well-known principles of servo-mechanical control.

The phenomenon is worthy of special attention in studies of speech perception in noise. If recorded or monitored speech is used, the most serviceable data will be obtained only if the speech is delivered at a level found by experiment to be appropriate to that of the noise.

As an interesting corollary to these findings it will be seen that they provide firm support for the well-known theory propounded, by Jenkins among others, as long ago as 1913: that the phenomenon of paracusis Willisii arises in part, at any rate, from the fact that the hard of hearing subject benefits from the raised voice level of the normal hearing speaker in noisy surroundings.

The voice level measurements described represent a special case of a large body of sounds which fall into the category of transient sounds. Their measurement calls for special techniques, and these will be considered briefly as follows:

Impact and explosive noises give rise to very high peak pressures, which cannot normally be measured with a sound level meter owing to the inertial lag of the mechanical moving parts of the indicating instrument. To overcome this difficulty, an auxiliary instrument has been developed, termed a peak indicator, which is used in conjunction with the sound level meter.

The peak sound pressure develops a charge across a condenser incorporated in this instrument, and the detection of this charge by the sound level meter indicates the overall energy in the noise.

The spectral analysis of transient sounds is, of course, made particularly difficult by their brevity. If the noise to be measured has a minimum duration of a second or so, it can conveniently be recorded upon magnetic tape. The tape can then be made into a loop, and played back as many times as is necessary for an analysis to be carried out in the laboratory in one of the ways described for steady sounds.

The cathode ray oscilloscope lends itself particularly well to the spectral analysis of transients, since its response is free from the inertia effects to which reference has been made. Good use has been made of it in an instrument termed the acoustical spectroscope. The sound to be measured is amplified and applied in turn by means of a mechanical drive to each of a number of 1/3 octave band filters covering the whole of the audible frequency range. The output from each filter is displayed as a vertical band upon the face of the cathode ray tube, each frequency band being identified by an engraved scale immediately below the face of the tube. The whole spectrum can thus be sampled many times a second, resulting in an instantaneous picture of the spectral composition of the sound.

It has been the aim of this communication to outline some of the more important problems which confront the acoustical engineer, and it cannot be claimed that the field has been covered exhaustively.

Many problems remain; of these perhaps the most urgent are to be found in the overlapping fields of physics, psychology and physiology.

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Professor W. Burns (Department of Physiology, Charing Cross Hospital Medical School):

Noise and Its Effects: Physiological Aspects

Introduction.—It is of interest that hearing loss from noise has been recognized at least since the latter part of the eighteenth century. Parry (1755–1822) describes cases (1825) which, at least superficially, conform to the characteristics of temporary and permanent hearing loss due to exposure to noise. In one incident, Admiral Lord Rodney is described as being almost entirely deaf for fourteen days following the firing of eighty broadsides from his ship, H.M.S. *Formidable*, in the year 1782. The other case is that of an officer who was stated to have been rendered permanently deaf by the near-by discharge of a cannon at the battle of Copenhagen. The problems of aural damage as a result of noise are still present, and in a much more acute form since those days; man-made noise has greatly increased in extent and in intensity, and it has become a problem of some urgency to study the relations between the noise and the effects by all available means, in order to control and minimize damage to hearing. The approach to this problem can broadly be made in three ways: the reaction to noise exposure of individual ears can be followed in practical situations by clinical methods, including that of pure-tone audiometry; the effects of specific noise stimulation can be studied in psycho-acoustic experiments; or stimulation of the ears of experimental animals may be preceded and followed by the use of some technique, psychological or physiological, which will detect changes in the response of the ear. Only the last method will be considered here.

Aural damage from sound.—Different types of hearing loss may affect the human ear as a result of sound stimulation. First, we may have temporary loss of various degrees of severity, which, at least, may be transitory and only detectable by special means or, at worst, may persist for hours or days. Greater severity of exposure to sound may produce permanent loss (usually combined with some degree of temporary loss) and this may arise from moderate sound levels, applied for months or years in the course of work, or from a single damaging exposure, such as a detonation or a very intense noise lasting for a period of the order of minutes or hours. These distinctions are of importance in the physiological approach, for some of these effects are more suitable than others for investigation by physiological means, as will be discussed later. In the present context only damage to the cochlea itself is considered; tympanic membrane and middle ear effects are ignored.

Physiological criteria of cochlear function.—In assessing the suitability of various physiological criteria as indications of the effect of noise on the ear, it is useful to recall some of the current beliefs on the fundamental features of cochlear function. The criteria relevant to this discussion are the electrical potentials known as the cochlear microphonic (CM) and the action potential of the auditory nerve (AP). In order to examine these phenomena in more detail it is desirable briefly to consider the movement of the basilar membrane when sound falls on the ear.

Movements of the basilar membrane.—Since the concept of Helmholtz, formulated in 1863, that the cochlea contained structures capable of resonating to different frequencies in a highly selective manner, some changes have occurred in our approach to the physics of cochlear function. The majority of current opinions regard the cochlea as a number of canals, partially bounded by elastic walls, in which wave motion akin to the pulse-wave in arteries is generated by movement of the stapes. A number of mathematical formulations have been built on these lines, varying in detail according to the assumptions made, but direct examination of the mode of vibration of the cochlear partition, i.e. basilar, tectorial and Reissner's membranes, has been made by Békésy (1949), using human cochleæ in suitably prepared temporal bones. This technique involves the replacement of the stapes by an electrically driven piston, which can be moved at known frequencies and amplitudes of vibration. The resultant movements of the cochlear partition are studied microscopically with stroboscopic illumination, through small windows in the bony wall, with precautions to ensure that the presence of the windows does not affect the result. These techniques showed that, in general, all the components of the cochlear partition, i.e. the basilar membrane, the organ of Corti, the tectorial membrane, and Reissner's membrane, vibrate in the same phase when the stapes vibrates. At frequencies of less than 50 c/s the entire cochlear partition vibrates at this frequency, and the vibration is practically in phase for the whole partition. At higher frequencies, travelling waves can be demonstrated, originating at the base of the cochlea, and travelling towards the apex. These waves increase in amplitude as they traverse the cochlea, finally reaching a maximum amplitude and then subsiding relatively suddenly, the maximum occurring at a distance from the base of the cochlea, characteristic of the particular frequency. The highest frequencies reach their maximum amplitude nearest the base of the cochlea, the waves due to lesser frequencies reaching progressively farther towards the apex before reaching their maximum. The relationships of frequency, phase, amplitude and

conduction velocity of the waves are complex, and are conveniently summarized by Békésy and Rosenblith (1951).

The cochlear microphonic.—It is now possible to obtain information about the action of the organ of Corti, and more indirectly about the movements of the basilar membrane, by a study of the cochlear microphonic, hereafter referred to as CM. This is an electrical potential which can be recorded, when sound reaches the ear, from a variety of sources in the cochlear region, for instance by an electrode placed on the round window and referred to an indifferent electrode on the neck of the animal. Much information has been obtained by a study of CM and its relations to sound stimuli (Stevens and Davis, 1938; Wever, 1949). The CM is found to resemble closely the sound stimulus applied to the ear, and thus is equivalent to the electrical output of a microphone. It does not resemble the potentials due to nerve activity, as is well known. It appears to be generated by the hair cells in response to movement of the organ of Corti, and particularly in the hands of Davis and his associates has become a very useful index of cochlear activity. Tasaki *et al.* (1952) have evolved a technique in which CM can be recorded simultaneously with the action potential of the auditory nerve, each electrically separated from the other. This technique employs very fine wire electrodes which are inserted into the canals of the cochlea; a pair of these electrodes can be used to obtain the potential across the cochlear partition by insertion into scala vestibuli and tympani of a particular turn of the cochlea. In this case CM can be recorded from a length of the cochlea in the order of 1 or 2 mm., so conferring an immense advantage over other methods because of the precise localization of function thus made possible.

By these means Tasaki *et al.* have shown that Békésy's conclusions, with regard to the action of the human cochlear partition when thrown into vibration by sound, can be confirmed for the guinea-pig cochlea. Thus, by examination of the amplitudes and phase relations of CM in two or more turns of the cochlea in response to various frequencies of sound stimulation, they demonstrated the occurrence of travelling waves which pass along the cochlea from base to apex, for a distance which is greater the lower the frequency of sound incident upon the ear. Their results only differ from those of Békésy on the movements of the human cochlear partition, in the apparently greater vibrational amplitude as judged by the voltage of CM in the basal regions of the cochlea. As in Békésy's mechanical study, the CM was little affected by deficiencies in the bony wall of the cochlea.

Of particular interest for the study of the effects of acoustic stimulation of the cochlea are the relationships of sound input to cochlear microphonic. Among the many complex relationships described by Tasaki *et al.*, an important one is the relation between sound pressure level of the sound stimulus and the voltage of the cochlear microphonic, measured at an appropriate part of the cochlea. The result is in conformity with earlier measurement of CM between the round window and an indifferent electrode placed on the neck of the animal, and shows that CM voltage is related linearly to the sound pressure levels, up to sound intensities at which CM either reaches a maximum and then declines, or else the waveform becomes too distorted for proper measurement. In addition, the "threshold" of CM can be determined for any particular frequency (Davis and associates, 1953); this is not the true threshold, but a sound level at which the presence of a recognizable CM waveform begins to be visible against the background oscillations of the output of the amplifying system. By utilizing this criterion a form of electrical audiogram of the guinea-pig ear may be obtained, but with the differential electrode system of Tasaki *et al.* the electrodes must, of course, be inserted into the part of the cochlea appropriate to the sound frequency used; for example, high frequencies will not produce CM voltages at the apex of the cochlea.

The action potential of the auditory nerve.—In the past, electrical changes due to the combined effect of the action potentials of all the active fibres in the auditory nerve, hereafter known as AP, were a feature of the classical round window records, and indeed of the original observations of Wever and Bray (1930), in which they appear combined with CM. By the differential method of recording, they can be separated from the CM oscillations, as stated above, and appear as a pure AP waveform, as if an electrode had been applied to the auditory nerve at the internal auditory meatus. In order to produce a well-marked action potential wave, by approximately synchronous activity in the active fibres, some form of brief acoustic stimulus is necessary. For this purpose a sound usually referred to as a click may be used; this is produced by applying a short square-wave electrical pulse to the coil of a loud-speaker. Alternatively, short duration pure tones, known as tone-pips, have been used by Davis and associates (1953), for the same purpose. When these are used, in records both from the round window or by the differential method, the "threshold" sound pressure may be determined for the ears of anæsthetized animals in acute experiments, again by presenting a series of acoustic stimuli at progressively increased intensity until AP is just visible on the oscillograph trace against the background oscillations. The size of AP will depend, among other factors, on the number of active fibres. The relationship between the stimulating

sound and the evoked nerve activity deserve, and are receiving, further attention at the present time.

Effect of efferent activity in the auditory nerve on the afferent output from the cochlea.—There is one other factor which may be of considerable importance in the interpretation of cochlear activity. Galambos (1956) has now shown beyond doubt that the afferent nerve discharge from the cochlea may be reduced or inhibited by electrical stimulation of the medulla; and moreover, that the effect appears to be mediated through the olivo-cochlear bundle described by Rasmussen (1946). These results were obtained by presenting click stimuli to the ear of the decerebrate or anæsthetized cat, and recording the electrical activity so caused from the round window. The electrical output contains both CM and AP, and it is noteworthy that, although AP may be reduced or abolished by stimulations of the medulla, the size of CM is unchanged. The great potential importance of these phenomena need not be emphasized, and it is of interest to note that there are other sense organs whose sensitivity is not invariable, but adjustable through the operation of pathways carrying efferent impulses from the central parts of the nervous system; such a system is of great importance, for instance, in the control of skeletal muscle, by discharge from muscle spindles.

Indices of cochlear function following intense sound.—Having looked briefly at the phenomena which are potentially useful in a physiological approach to the study of the effects of intense sound on the ear, we may now consider how they may be used for this purpose. The basic operation is to determine certain characteristics of the normal ear, to subject it to sound stimulation, and then to repeat the initial observations. As a result of work of this sort, as described by Wever (1949) and by Davis and associates (1953) it has become evident that the type of electrical index must be appropriate to the type of sound exposures used. For severe or damaging exposures, CM provides a useful guide, due to the fact that severe exposures are required to produce appreciable reductions in CM voltage. It may with advantage be used in conjunction with histological examination of the exposed cochlea. On the other hand, for the study of transient effects following less intense stimulation, and corresponding to temporary hearing losses, the more sensitive and labile AP provides a more suitable index, and has been so used by Rosenblith *et al.* (1950), by Rosenblith (1950) and by Davis and associates (1953), and by others. These techniques may now be examined in greater detail.

The cochlear microphonic as an index of acoustic trauma.—The differential recording system of Tasaki *et al.* is admirably suited to an examination of the local effects of intense stimulation by pure tones, and this has been combined with histological examination of the cochleæ of guinea-pigs so exposed, by Davis and associates (1953). It is well to emphasize again that the electrode position must be appropriate to the frequency of sound stimulation in order to assess changes of CM following such stimulation. It is not possible in the scope of this brief review to cover adequately the details of this work, but the essential findings showed that CM is a reliable index of damage to the cochlea. It was found that, following sound stimulations, the "threshold" of CM was elevated in terms of db., by twice the amount of the reduction in "maximum" voltage of CM, produced by an arbitrary high level of sound stimulation. The extent of these reductions was compared with an arbitrary numerical scale describing the observed degree of damage to hair cells and supporting structures in the cochlea. The effects ranged from minor changes in the cellular structure to gross disruption, breakage and displacement, and it was found that the extent of change of CM voltage or threshold was consistently related to the numerical scale of damage. The injuries caused by tones of 8,000 c/s centred in the basal turn, 2,000 c/s in the second, 545 c/s in the third and 185 c/s tones at the junction of the third and fourth turns; no pure tones at these frequencies and at intensities up to 148 db., and durations of the order of 5 minutes or less, damaged the entire cochlea. It was also found at the highest intensities (about 144 db. at the eardrum) that an exposure to one minute at any of the four frequencies used produced equal degrees of cochlear damage. In assessing the probable implications of these results for the human ear, the authors believe that the human ear is similar in strength and resistance to damage to that of the guinea-pig and in general that for given amplitudes of the stapes in the oval window, it could probably be assumed that the damage to human ears would be similar to that found in the guinea-pig ears, except at the lowest frequencies, where the intra-aural reflex may give appreciable protection in man.

Auditory nerve action potential as an index.—For the study of transitory after-effects of sound upon the ear AP may be elicited by brief test stimuli such as clicks at some arbitrary sound level, in the manner just described; following this, the fatiguing tone or noise is applied, and the test stimuli resumed at the same intensity as before. The "threshold" of the ear may be determined on the basis of a just visible AP, or the effect of the fatiguing tone followed by using the amplitude of the AP wave as an indication of the neural activity. Rosenblith *et al.* (1950) have employed such means in the cat, using click stimuli and recording

the combined CM and AP from the round window. It was found that exposure to loud tones reduced the size of AP immediately after the fatiguing tone, and that the rate and mode of recovery depended on the intensity, the frequency and the duration of the fatiguing tone. During these changes in AP, CM shows relatively little change. Rosenblith (1950) describes further applications of this technique; the recovery rate of AP can be quantified by expressing the size of the post-exposure waveform as a percentage of the pre-exposure size, which permits the construction of a graph of recovery of AP as a function of time after the end of the fatiguing tone. If this method has any similarity to psycho-acoustic experiments on the recovery from temporary hearing loss, one would expect a restoration of the pre-exposure characteristics of AP in a period of the order of minutes after moderate exposures, and this is indeed found to be so. Further, the exposure to click stimuli would appear to indicate that the temporary impairment is more severe when the test stimuli (clicks) are weak, than when they are presented at a high intensity. In the latter case little or no reduction in size of AP may be found, and this provides an interesting comparison with the situation in human deafness in which recruitment is present, and in the work of Davis *et al.* (1950) whose experimental exposure to loud tones or noise was followed by a much greater depression of the threshold sensitivity than of the apparent loudness of tones.

These illustrations indicate the lines along which investigation may be pursued. The basic need at present is to provide a better understanding of the physiological processes underlying the reaction of the human ear following various kinds of acoustic stimulus. Enough is known to enjoin great caution in comparing the situations involved in acute acoustic trauma, long-term hearing loss of the occupational sort, and temporary hearing loss. As Davis and associates (1953) point out, and the same is true at this time, our knowledge of the physiological processes involved is still insufficient to justify theoretically the use of some test of temporary hearing loss, as an indication of susceptibility to long-term industrial permanent hearing loss. Work continues in these fields, however, and one may anticipate further elucidation of the basic physiological reactions to sounds which, in one way or another, may be potentially damaging to the functional integrity of the ear.

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Mr. D. E. Broadbent (Applied Psychology Research Unit, Cambridge):

Noise and Behaviour

There are three kinds of psychological experiment to be discussed in this paper: that is, three kinds of experiment on the behaviour of intact human beings. The first kind is really an extension of physiology, because it is aimed at finding how much a man's hearing has been damaged by noise. Instead of examining the damaged tissues in the ear directly, however, the method is to study the effects in behaviour: in other words, the change in the threshold of hearing. The second kind of experiment to be mentioned will be researches on the way in which speech perception is affected by losing hearing in particular frequency bands, which is a common effect of noise exposure. The third group of experiments will be those on the efficiency of work in noise, which is more nearly what is usually meant by a psychological effect.

To start with the question of deafness, most of us are not surprised when a man who announces himself as a boilermaker or an artilleryman, proves to have a poor audiogram. This kind of common-sense impression is a little dangerous, perhaps; because a man with a history of years of work in noisy places has to be fairly old. People do get more deaf as they get older, and so one must beware in case one's clinical impression is comparing boiler-makers of 50 with sprightly young apprentices of 18. The average man of 50 has in any case lost 20 db. at 4,000 c/s, according to several large-scale surveys.

But there are now a number of researches which have allowed for age and which have demonstrated that people with noisy work can hear less than people of the same age with

quiet work. For instance, Guild (1951), showed that U.S. Air Force aircraft mechanics had poorer hearing than members of the Air Force who worked in comparatively quiet places. Out of men in the 25–29 group, less than half the mechanics had normal hearing, or only slight loss, while amongst men of the same age working in quiet, over 80% were normal. In this country, Johnston (1953) studied seven kinds of work having different noise levels, and found an increase in the proportion of people with hearing loss as the noise increased, provided the people had at least twenty years' exposure to the noise. Hearing loss in this case was detected by requiring the patient to understand speech at 3 feet distance which is hardly a sensitive test. It makes the finding that 9 out of 12 workers in the worst noise had a hearing loss by this test, rather an alarming one. Their loss was really noticeable.

But these rather general investigations do little more than confirm our original opinion that deafness due to noise is of practical importance, and is not simply an effect which laboratory researchers play with for want of something better to do. Given that the effect is important in practice, we want to know what frequencies are dangerous and how loud the noise has to be to produce deafness. Some data on this have at last become available, thanks to the American Standards Association (1954); and in particular to their Subcommittee which rejoices in the title of Z24X2. Dr. Wayne Rudmose, on behalf of this Subcommittee, visited a number of factories and took 7,000 audiograms from the workers. He then examined those cases in which the intensity and spectra of the noise were known, the length of exposure to the noise was known, and the worker was not known to have been exposed to any other loud noise. This cut the 7,000 down to 200, which is, of course, why nobody had done research of comparable scope previously.

Two hundred people are sufficient for certain valuable conclusions. For instance, one can correlate deafness at a particular frequency with noise exposure at that frequency, or at frequencies one octave lower or higher, two octaves and so on. If one does this one finds that deafness at 4,000 c/s doesn't seem to be closely related to the amount of noise of 300 c/s to which the individual has been subjected. The best predictor of deafness at 4,000 c/s is the amount of noise in the octave from 1,200 to 2,400. Correspondingly the best predictor of deafness at 1,000 c/s is the amount of noise in the octave from 300 to 600. In other words, noise of a particular frequency seems to be related to deafness at a slightly higher frequency. This agrees with laboratory experiments on temporary deafness, in which at high intensities the deafness shifts upwards in frequency from the stimulus frequency to a higher one.

At the same time, it is still true that the 4,000 c/s region is more easily affected by noise. If you have worked for ten years in a noise having 88 db. in the octave centred on 1,800 c/s, your hearing at 4,000 c/s will be almost 25 db. down (on the average). If you had had a comparable exposure in the octave centred on 450 c/s, your hearing at 1,000 c/s would be only 5 db. down. If you want to keep the noise down to the point at which the loss of hearing as the years go by is merely the average for the community at large, then you can have 80 db. in the octave centred on 450 c/s, but only 73 db. in the octave centred on 1,800 c/s. In summary, the 4,000 c/s region is definitely more susceptible to noise, but deafness to a particular frequency is largely a question of exposure to noise of a particular frequency band rather below that at which the deafness occurs. Measuring simply the total level of a noise tells us very little about its deafening qualities: the spectrum is also necessary.

The safe levels per octave which I mentioned earlier are very low: many industrial processes exceed them. It would be very valuable if one could pick out the tenderest ears from a group of workers before they were damaged, so that the remaining people could work in a rather higher level. A start has been made in this problem by Jerger and Carhart (1956) who measured temporary deafness from a one-minute exposure on a group of people who afterwards worked in jet-engine noise for a period which exposed them to the risk of permanent deafness. The people who had the biggest temporary deafness were, on the whole, the ones who afterwards suffered the greatest permanent harm. Unfortunately, the relationship was not as close as one would like, some people with a small permanent loss having had a large temporary one; this may be because the permanent deafness was not in any case very considerable, or possibly because of some particular feature of the technique of measuring temporary deafness. After being temporarily deafened, the victim had to listen until he recovered enough to hear a pulsed tone of standard intensity: which often meant listening for ten or fifteen seconds before responding. It may be that wandering of attention would introduce a random element into the results of such a test which would not be present in other techniques. In any case, the possibility of using deliberately produced temporary deafness to pick out susceptible people is one which is well worth pursuing.

Now, what effect does this type of deafness have on speech perception? Nobody seems to have studied the kind of mistakes which are made by people with certain kinds of deafness, but there is a good deal of recent information about the effects on speech of various kinds of distorting telephone line, and these seem to be rather relevant. Admittedly the kind of deafness produced by noise is not simply a removal of the ability to hear high frequencies,

since there is also a distortion of the loudness of sounds which are intense enough to be audible. Still, the effects of removing high frequencies from a telephone circuit are likely to have some similarity to those of deafening a man to high frequencies while leaving the lower ones unimpaired. And noise, as we have seen, does produce rather that effect.

If we consider the consonants usually written as p, t, and k, we find that they are produced in the same sort of way but in different parts of the mouth. P as in "pen" is in the front, t as in "ten" farther back, and k as in "ken" farther back still. This difference in the place of articulation produces a difference in the sound, so that a listener can tell which consonant has been said. The same kind of difference exists between b, d and g, between f, s and sh, between v, z and j, and between m, n and ng (I use ordinary letters although really phonetic symbols would be more accurate). Now how do we tell the difference between these groups, since the place of articulation distinguishes only within them? How do we tell p from b, or f from v? Well, in b and v the vocal chords vibrate while in p and f they do not: the consonants are said to be voiced and unvoiced correspondingly. And the difference between b and v, or between p and f, consists of the presence or absence of fricative noise. Consonants can therefore be placed in an interlocking classification, and it has recently been shown by Miller and Nicely (1955) that removing the high frequencies from speech affects chiefly the discrimination of place of articulation. The presence or absence of fricative noise is more easily distinguished, and the occurrence of voicing is the least affected by losing the high frequencies. The words "pat" and "bat" for instance, can be distinguished using low-frequency hearing, but the distinction between such words as "pop" and "tot" requires high-frequency hearing (Table I).

TABLE I.—DISTINCTIONS BETWEEN CONSONANTS

	No fricative noise	Fricative noise
Unvoiced..	PTK	FS SH
Voiced ..	BDG	VZ J

Consonants within each cell differ in place of articulation and are likely to be confused by people relying on low-frequency hearing. Confusions between right and left, and particularly between upper and lower cells, are unlikely. Ordinary consonants are used for expository purposes: phonetic symbols would be more accurate.

There is hardly time to go into it, but the work of F. S. Cooper and his associates (1952), using artificially generated speech sounds, gives some explanation for this finding of Miller and Nicely. Crudely, when one makes a vowel such as "ar" in "par" or "tar", at the very beginning of the vowel one's tongue has to rush across the mouth in a way which depends on the place at which the previous consonant was articulated. This means that the very beginning of the upper harmonics of the vowel are different when the preceding consonant is a p from those which follow a t. The difference is rather a high-frequency one, while the effect of voicing is to introduce a low-frequency component which is particularly difficult to mask. Yet whatever the explanation, the practical importance of these findings is that people deafened to certain frequencies by noise exposure are likely to have rather specific difficulties in understanding speech: some statements they will understand perfectly. And, as Miller and Nicely point out, the place of articulation which is the most likely feature of consonants to cause difficulty, is the easiest feature to detect by lip-reading. As a result the advantages of lip-reading to the noise-deafened will be greater than one might imagine at first sight.

In considering the effects of noise on behaviour which does not involve hearing, we should distinguish annoyance by noise from a direct effect on efficiency. Annoyance often results from some feature of the individual's past experience. For instance, in a recent survey of complaints about aircraft noise, it was found that over 80% of the people who complained had some reported anxiety about aeroplanes—they would not fly themselves, or they were frightened of aircraft crashing on the house (C.H.A.B.A., 1954). One can make rough rules, such as that the proportion of people who are annoyed will rise as the noise becomes louder, or that a noise which seems to be preventable will produce more complaints than one which is normally regarded as inevitable. But the reduction of annoyance remains rather an empirical art.

Until recently it was thought likely that the only effect of noise on working efficiency was the indirect one that it might irritate and annoy the workers, a matter which could perhaps, if necessary, be countered by higher pay or a better canteen. But it now seems established that particular kinds of work are affected in a particular way by noise, even though other kinds of work may not be. There are two effects which have been shown. First, if a man is watching for some rather insignificant event to happen, such as a faint spot of light to appear in a gun-sight, and if he does not know when this event is going to occur, he will take longer to respond to it when working in a noise. Second, in a very continuous task allowing no breaks for rest, momentary errors and aberrations will occur in noise although work between these errors will be quite unaffected. For instance, if one is keeping count of three streams of parts going past on three conveyor belts and must take action every time ten parts have gone by on any particular belt, one is likely to make some mistakes in noise.

Both these effects will only appear if one has been working for some time in the noise. These effects were originally somewhat doubtful, resting on one group of experiments done in a Cambridge laboratory (Broadbent, 1953, 1954), but they have now been confirmed by two research centres on the other side of the Atlantic, which makes them more universal in their application. The task for keeping count of several streams of events was devised by H. J. Jerison (1954) working for the U.S. Air Force. The American workers have also pointed out the interesting fact that judgments of time-intervals are very badly distorted by noise (Smith *et al.*, 1955). None of these effects has been shown with noises of less than 90 db.

Now why do these rather specific effects appear although noise produces no effect on, for instance, the time taken to sort cards or the score on an intelligence test? I personally find it helpful to draw an analogy with the familiar process of blinking. Every time you blink you produce an interruption of the flow of visual information into your brain. Yet the interruption is a short one, and in any case blinking can be suspended while one does a *short* job requiring close attention, the necessary blinks being made at some other time when nothing is likely to happen. For instance, it is known that a driver blinks less in heavy traffic than on the open road. And in addition, work on familiar tasks can often be done without taking in information at all; a real yachtsman can tie knots on a dark night with his fingers numbed with cold. Blinking, therefore, scarcely affects the efficiency of work.

I think myself that there is a process like blinking but located between the sense-organs and the main body of the nervous system, and producing interruptions of the flow of incoming information which last perhaps a second rather than the small fraction of a second taken by true blinks. These internal blinks are supposed to be increased in frequency by noise, and they would produce just the effects on behaviour which are in fact observed. There would be no effect on short tasks nor on those which contain periods in which the worker knows that nothing will happen. But there would be a delay in noticing unexpected events, and there would be momentary errors in responding to a truly continuous stream of stimuli. There is a good deal of supporting evidence for his view. To take a physiological, though indirect, example, it has been claimed by Hernández-Péon and his associates (1956) that the usual cochlear nucleus response to click sounds disappears when the cat from which recordings are taken is shown a mouse. This is exactly the sort of mechanism which I have called an "internal blink". The kind of work likely to be affected by noise is the kind which would be affected by blinks if each blink lasted a second. Very often this means that accidents and scrappage rather than output will be the danger sign in industrial situations.

All this recent knowledge about noise warns us, in fact, that we must not be provoked by the overstatements of those who find noise annoying, into denying that it affects human beings. It does do so, to a limited and increasingly well-understood extent, and we should guard against it.

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Dr. H. F. Schuknecht (Detroit) delivered a paper on **Deafness following Blows to the Head** (see *Arch. Otolaryng., Chicago* (1956) **63,** 513).

[*February* 1, 1957]

A discussion was held on **Irradiation of the Nasopharynx;** the opening paper was read by Dr. G. Aschan and was entitled Histopathology of Otosalpingitis as a Background for Deep X-ray Treatment. Mr. W. Stirk Adams gave the Report of the Medical Research Council Team and Mr. J. Angell James read a paper on Irradiation Treatment of Recurrent Otitis Media.

The President, Air Vice-Marshal E. D. D. Dickson, Wing Commander P. F. Ewing, Mr. J. Chalmers Ballantyne, Mr. R. F. Martin, Mr. G. H. Bateman, Mr. T. R. Mawson, Mr. Brian Reeves, Mr. I. Simson Hall and Mr. C. R. Salkeld took part in the subsequent discussion to which Dr. Aschan and Mr. Stirk Adams replied.

The meeting will be reported in the *Journal of Laryngology*.

Section of the History of Medicine

President—DOUGLAS GUTHRIE, M.D., F.R.C.S.Ed., F.R.S.Ed.

[*November* 7, 1956]

Medicine and Dentistry in Newcastle Upon Tyne in the Eighteenth Century

By JOHN BOYES, F.R.C.S.Ed.

Professor of Oral Surgery, University of Durham

NEWCASTLE is an old town by most standards of antiquity with a long and fascinating history and there are still places of great charm to remind us of former days. The castle and St. Nicholas' Cathedral with the beautiful lantern tower are the best known.

The Company of Barber Surgeons of Newcastle upon Tyne is another link with mediæval times. Unhappily its membership has dwindled to a handful and it is almost certainly destined for extinction despite the valiant attempts to resuscitate it by Professor F. C. Pybus and the late Professor Grey Turner. This is the oldest Newcastle Medical Institution and Newcastle and London are the only towns in the country where such a Company still exists.

The activities of the Barber Surgeons Company in the 18th century were quite varied. In addition to the particular matters affecting the Surgeons they contributed generously to a number of local and distant charities; for instance in 1740 they sent 10 guineas to the Edinburgh Infirmary. Part of the enjoyment of historical enquiry is the occasion which it affords for speculation. The explanation of this donation is probably the wide appeal which was made at that time on behalf of the Edinburgh Infirmary. (The success of the appeal enabled the Infirmary to be accommodated in a new building the following year.) However, on searching through the Newcastle papers in the 1720s I noticed annually for a number of years the announcement of the commencement of the Medical Course in the College in Edinburgh, and I wondered if some of the surgeons of the Company had gone to Edinburgh and studied surgery and anatomy under Alexander Monro primus and thereby had a partiality for Edinburgh medicine.

During the serious corn riots of 1740 the surgeons of Newcastle took turn to be on civic guard. By a majority vote they offered their Hall to the town during the active military preparations at the time of the '45. It was thought that the Hall would provide adequate accommodation for officers. As dissections were done in the Barber Surgeons' Hall, one imagines it was rather a grim place in which to be billeted.

In 1758 Richard Lambert, surgeon to the Infirmary, announced that he would begin a course of Anatomical and Chirurgical lectures at the Surgeons' Hall, Newcastle. I do not know if this course was ever held as it was never advertised again. Dr. Wilson gave a course of lectures in Medicine in 1767 at his own house in Rosemary Lane.

In 1724 William Prior, a musical instrument maker, moved from Gateshead to Newcastle and in a house at the head of the Side, set up business and designated his trade by signing his shop with a musical instrument. Ten years later he organized a raffle: "On Tuesday, 22nd October 1734 next at the house of William Prior there will be raffled for a new organ, concert pitch, fit for church, chapel or chamber, with two sets of keys, long eights and eight stops, viz: open diapason, stop diapason, principle, flute, 15th, cornet, sesque alto and trumpet so contained that four of the said stops with proper handles all are played upon the lower set of keys and for greater variety several of the stops draw in halves. There will be 100 lots or no raffle. Price of each lot to subscribers, one guinea.

The said organ may be on view every day till the time of the raffle begins at Mr. riors which will be at 1.0 o'clock in the afternoon of the aforesaid day."

However, it is his 1724 announcement that is of interest. In it he states that h sells all types of musical and mathematical instruments, music books of tunes and song and he does turning work at reasonable rates, and then the important thing—"he also makes and sets artificial teeth so neatly as not to be discovered from natural ones". Fifteen years later William Prior advertised in the first number of the *Newcastle Journal* which was published on April 7, 1739, and this time his advertisement was largely dental.

"Artificial teeth set in so firm as to eat with them and so exact as not to be distinguished from natural. They need not be taken out at night as is by some falsely suggested but may be worn years together. They are so fitted as to be taken out and put in at pleasure by the person who wears them and are an ornament to the mouth and greatly helpful to the speech. Also musical and mathematical instruments are made and all sorts of turning done by William Prior at Whitefriars at the foot of Westgate, Newcastle."

The medical advertisements in the early press are of interest and give some indication of common ailments. In 1721 we find Tipping's Pleasant Liquor advertised. This "dissolves the stone in the bladder or kidneys, bringing it away visibly with whatever gravel may be generated in those parts and gives ease in the colic as likewise the pains of the gout and rheumatism and soon after restores the use of limbs and is only sold at Harrison's Coffee House at the Sandhill, in Newcastle at 3/6d. a bottle". Again, there is The Most Excellent Cephalic Water or Liquid Snuff which was prepared for her late Majesty Queen Mary and published "by her authority". "It is the brain's best friend in curing all its diseases as all violent headaches, apoplexies, epilepsies, migranes, vertigos and swimmings in the head etc., price 6d. per bottle."

I wonder what the citizens of Newcastle thought on reading in 1720 "whereas many thousands die yearly of worms only, more than any other distemper whatsoever, and as all persons of all ages are incident to them even from birth to old age and as they are the inlet of most distempers and as Dr. Lucas' remedies of Newcastle have been tried and found by the experience of many hundreds to exceed any others yet known for killing and destroying of worms and the cause thereof in old and young and has never yet failed in its designed end by bringing away worms of various sizes and shape some from children of six or seven years old and upwards of 7 yards long at the Doctor's house to be seen. The medicines are as pleasant as sugar candy and as safe as white bread. They may be given to a child of three months old. Also for the further good of mankind is published the doctor's chemical preparation for killing the toothache without drawing, and scurvy in the gums by giving immediate ease in the most tormenting pains and carrying off the sharp humour which falls from the teeth and gums. Also it fastens loose teeth and causes the gums to grow afresh although eaten away with the very scurvy and those who use it are seldom or never troubled with the toothache any more where it is applied, so that a person may by these methods preserve all their teeth fair and sound even to an old age, price 1s. 0d. a bottle with full directions, sold at the Doctor's house in Pilgrim Street, in Newcastle over against Silver Street end, a ball being over the door where may be had his powder for the stone and gravel, strangury and stoppage of the urine, also his tincture of gold that cures rheumatism and weakness in the body or limbs".

Dr. Lucas died in 1720, a few weeks after the publication of the advertisement just quoted, but his wife was in the secret for she says: "These are to acquaint the public that the doctor faithfully communicated every secret of his medical preparations to his spouse who had upwards of ten years' experience in their preparation" and she goes on to say that "the preparations are just the same as if the doctor were now living."

In the edition of the *Newcastle Courant* of February 9, 1723, there can be read the following: "Whereas the smallpox and very dangerous sort of fever have for a considerable time raged with much violence in the town of Newcastle upon Tyne and other neighbouring towns and has been attended with great mortality, this is to give notice that there is a medium discovered which after immense trials has never been known to fail of curing persons afflicted with either of these fatal distempers, even when all other means used for their recovery have proved ineffectual and very often when they have been in all appearances at the last gasp and given over by those who have attended them, which medicine was discovered and now prepared only by Mr. Thorauld, master of mathematics and student in physick next door to the Mayor's house in Newcastle aforesaid. This wonderful medicine being known to no other person living and never before made public but now advertised for the general good of mankind at the pressing instance and request of several of the principal inhabitants of the said town who have seen and experienced the surprising effects thereof."

Accidents of severity are reported from time to time in the papers. For instance in October 1724 "about 7.0 o'clock in the evening, a fire broke out in the house of Joseph Partis, merchant, which burnt down that part of it by the great church and the neighbouring houses were in the utmost danger but saved by the great care and vigilance of the Right Worshipful William Carr Esq., Mayor and other of our Magistrates, but the most dreadful accident in the conclusion by a quantity of gunpowder which had lain in the garret and the people having no notice of it, it took fire when part of the house was blown up and several men and women were killed upon the spot. Others have died since of their wounds and a great many labour under great uneasiness occasioned by this fatal blast. The cries and shouts of the people were scarce to be endured which continued about an hour, women running as distracted seeking for their husbands, children etc., and everyone seemed to be in the utmost confusion. The Mayor and several of the Aldermen were hurt and were in great hazard who having ordered the surgeons to take care of the several persons who are wounded and given £50 as a reward to those who were most diligent and active in extinguishing the fire". Newcastle employed a town surgeon who was paid £50 per annum but it is obvious that he alone could not cope with an accident of such magnitude.

Another well-remembered accident occurred in October 1750. It was reported as follows in the *Courant:* "On Saturday last in the afternoon as the Leed's wagon was going down the Side, the wheel chain broke which caused it to run with great swiftness and notwithstanding all possible precautions taken by the waggoner to prevent mischief, one Barbara Saunders wife of a nailor at Dunston was run over by which one of her legs was sore shattered and she was otherwise very much bruised. Soon after the accident her leg was cut off and we hear there are hopes of recovery." This accident was used in B.K.'s famous letter of December 28, 1750, and published in the *Newcastle Courant* January 6, 1751, which appealed for the establishment of a hospital to deal with injuries and sickness in the people of Newcastle, Northumberland and Durham. Here is his account of the accident:

"There was the case of that poor woman who had the misfortune but the other day to be run over by the Leed's wagon and whom I am told lay 5 or 6 hours in an open shop in the utmost misery and anguish before a lodging could be found for her or any assistance given her." B.K.'s letter met with an immediate response and public activity on behalf of the new hospital was most energetic. Subscriptions poured in as did offers of gifts in kind and of professional services. The gifts in kind included bed linen, crockery, bricks for building the hospital and a quantity of lime; free professional services were offered by the Physicians and Surgeons; there were also given the proceeds from musical concerts and theatre performances. Within a period of less than five months the hospital was opened on May 23, 1751, in temporary accommodation in a house in a street called the Gallowgate, just outside the town wall. The day when the hospital was opened was one of the most important in the history of the town. The Magistrates and Council and all the prominent people of the town and of the two counties attended a service at St. Nicholas' Cathedral at 9.30 in the morning and thereafter walked in procession up the Bigg Market, along Newgate Street and through the New Gate to the hospital, and after an inspection watched the examination and admission of patients.

The history of the Infirmary has been so well told by Professor G. H. Hume and by Sir William Hume that little further need be said except to mention one of the intriguing problems of medical history in Newcastle which is, where is the exact location of this house in the Gallowgate? There would seem to be no doubt from contemporary maps that it must have been on the north-east side of the street and probably close to the New Gate. We know something of the house itself for in the house visitors' report of July 18, 1751, there is a recommendation that each ward should have a Bible, a Book of Common Prayer and the Whole Duty of Man. As the result of this recommendation six Bibles and six prayer books were bought forthwith. This would seem to indicate that there were six wards. Further confirmation of this supposition has also been found. When the Infirmary removed from the Gallowgate to the permanent buildings which were built on the Forth Banks, in October 1753, the house was rented to Mr. George Dunn of Blaydon. Early in January 1754 Mr. Dunn advertised as follows:

"To lett. The front part of the late Infirmary in Gallowgate consisting of six fire rooms, a cellar, with water in the yard and other conveniences. For further particulars inquire of George Dunn at his house in Gallowgate who will lett the same."

Through the kindness of the present owners of the property in the vicinity of the New Gate—Messrs. Scott and Turner—I have examined the old documents of the property but there is no trace of Mr. Wastell's ownership and he was the owner of the house which the Governors of the Infirmary rented. So the quest still has to be continued.

A house in the Gallowgate also was used for the first hospital in Newcastle for lunatics in 1763. Again, this house is unknown. The lunatic hospital was established as a result of a letter by "Benevolus", published in the *Newcastle Journal*. After a short period this institution moved to a specially built hospital nearby in Wardens Close. The surge in public opinion for the establishment of adequate medical services was by no means halted and soon afterwards St. Luke's Hospital for Lunatics was established for private patients. Before this the Lying-in Hospital was established in Rosemary Lane. The Newcastle Dispensary offering out-patient facilities was established in 1777 and a Society for helping poor expectant mothers in their own homes was founded a year or two earlier. A prominent worker for this Society was William Smith, surgeon and man-midwife. He was one of the medical staff of the Society. For many years Smith conducted courses of lectures and clinical practice in midwifery in Newcastle; the first, in which he was associated with Mr. Greenwell, was advertised to take place in 1756 at Mr. Greenwell's house, Without Newgate.

The mention of midwifery takes us easily, if perhaps surprisingly, to vaccination, for in the *Journal* of June 4, 1768, we read "Beatrice Macdonald, midwife, will begin a course of lectures on vaccination on Monday in the Race Week in the forenoon at her house in the Sandgate. Such as are now practicing or purpose to practice innoculation may by application to me be supplied with my preparation for the same which the faculty may be assured has been administered to thousands with never failing success, and far exceeds the pompus suttoniam of any other arcana in speedily and effectively removing every disagreeable symptom which may appear during the whole process of the disease, and am certain had they been administered even when a very putrid smallpox raged they would have been attended with success. N.B. Such of the advertising parties as have not been instructed with the care of a single patient will be instructed privately and immediately admitted into practice on the most reasonable terms. The poor in the neighbourhood of Sandgate innoculated gratis."

While smallpox inoculation was popular in 1768 it had been in the news much earlier. In September 1721 there is an account in the "News from London" column of the *Courant* of Mr. Maitland, the surgeon, inoculating for smallpox six criminals at Newgate Prison. "It has succeeded on the five who never before had them beyond all expectation and the surprise of the Physician who almost every day visited them. The sixth who had them about last Michaelmas in Newgate found no matter of alterations, the innoculations in his arms and legs continuing pale and dry from the beginning so that the whole has most successfully answered Dr. Timony's account of this practice and is perfectly agreeable to the experience and observations of some persons now in London of known credit and reputation who have seen the practice in Turkey. The malefactors on whom the experiment was made are to be soon pardoned."

Inoculation for smallpox again was news in 1723 when the local paper intimated that Mr. Ammand, a noted surgeon, inoculated the smallpox at Leicester House upon the young Prince William Augustus aged 2 years and 1 month.

We find an early intimation of a fever that raged throughout England in 1733. "Whereas the present distemper appearing in the shape of colds, agues and fevers rages so violently in every family within the bounds of mortality and in most counties in England, these are to certify the public that the most effectual medicine recommended by the most eminent physicians that has yet been experienced for same is Daffey's Original Elixir to be had from the printer of this paper."

The fever or the 'flu, whatever it was that struck this country as an epidemic, was severe. The London correspondent of the Newcastle paper reports that on February 1, 1733, "1,588 people died in London in a week, the greatest number known since the sickness in the year 1665, but it seems that infants and aged people suffered most". This epidemic also raged in Edinburgh about the same period, and the Newcastle paper quoted its Edinburgh correspondent as saying "A sickness continues here and in all the country around, so that scarce a family has escaped. It is attributed to the unwholesomeness of the weather there having been little frost and almost no snow at this season". Later in the same year there were great rain storms of unprecedented severity in South Scotland and the North of England. Even in the eighteenth century the weather was blamed for a great deal of their troubles.

There was plenty of rain and snow in January 1740—here is the account as published: "January 1740 the greatest storm of easterly wind and snow that can be remembered the violence of which did vast damage upon the river Tyne by vessels running foul of each other and breaking of cables and pulling the rings out of the ground. Upwards of 40 keels broke from their moorings and by the force of the wind were drove up to the bridge and sunk several wherrys, ships bows staving each other. . . . The same day in the evening

a woman going home to Gateshead Fell was found next day dead among the snow occasioned by her falling into a ditch where there was 7 ft. of snow." Unemployed keelmen were engaged by the Mayor to clear the streets of snow and Alderman Ridley "gave heaps of small coal to all poor people who could fetch them". A great number of poor families in Sandgate and other places were thought to have starved in the extreme cold. The Churchwardens of All Saints provided "plentiful dinners to the poor of the parish at the Manor House". "A pheasant was frozen to the ground near the town." We hear from Penrith that "a poor man was found lying upon the snow near that town, being carried into the town was let blood and that instant died".

Leaving the cold and snow let us move on twenty years to discover that in the pleasant autumn of 1760 "Michael Whitlock, operator for the teeth is at the Queen's Head, Mr. Hay's in Durham who intends to be at Newcastle on Sunday 28th September and to continue one week, and to be at Durham the week following and so to continue week about at both places. He is well known in most parts of England and Ireland for his extraordinary art in fixing artificial teeth in so exquisite and beautiful a manner as has baffled the most distinguishing penetration and of equal use in every respect. He cleans the blackest and foulest teeth in a few minutes rendering them as white as ivory, restoring the mouth to its wonted sweetness without pain. He dexterously displaces teeth and draws stumps almost imperceptibly so sunk within the gums that no other artist would attempt".

Fourteen years later another dentist, Charles Edward Whitlock, came to Newcastle and set up in practice in Newgate Street. He was perhaps the first semi-permanent dentist for I have not been able to find any other trace of Michael Whitlock. It is tempting to suppose that C. E. Whitlock was Michael's son. He announced his arrival in 1774 and towards the conclusion he says: "Those ladies and gentlemen who please to honour him with their commands (during the stay of the Comedians) are requested to favour him with them at Mrs. Gale's, Newgate Street." This reference to the theatre seemed to be interesting and I referred to the theatrical play-bills and to my pleasure I discovered that a member of the Company performing at the theatre in the Bigg Market was Mr. Whitlock. He never seemed to take a prominent part but this might well have been due to the fact that his dental practice occupied much of his time. During the first season he was given a benefit and the play that he selected was "As You Like It".

Mr. Whitlock appeared with the Company every year and in 1781 he managed the players. The Company had their ups and downs, including a burglary as the result of which they lost 80 volumes of plays. In 1785 it was announced that the Company would only be there for a short time, until April and it is rather surprising to find in the *Newcastle Chronicle* of April 30 the following announcement: "Mr. Whitlock, dentist, presents his respectful compliments to the ladies and gentlemen of Newcastle and begs leave to inform them that being under an indispensable necessity of quitting this place without a possibility of completing the various orders they have been pleased to honour him with, he intends to return about the middle of the second week in May in order to finish the business he is now obliged to leave undone as likewise to execute any such commands he may be favoured with in the interim. Those ladies and gentlemen whose orders he has received and which form a multitude of business he has not been able to comply with will be first attended to, others in the regular course. Mr. Whitlock embraces with deepest sense of gratitude this opportunity of returning his most unfeigned thanks to his friends and the public for the many favours confirmed upon him and assures them that nothing shall be wanting on his part to meet their future commands and approbation."

This seemed to indicate a rather hurried departure, the notice is dated April 15 and appears in the issue of the 30th. 1785 was an important year for him for he married Miss Elizabeth Kemble at York. She, too, was an actress and sister of the famous Mrs. Siddons and Mr. Stephen Kemble. Could this sudden departure have something to do with his marriage at York? Mr. Whitlock's wife joined the Company, acted in Newcastle and her first appearance was in February 1786. With Mr. Austin, Whitlock took over the management of the new Theatre Royal opened in 1788, a great occasion on which the bells of St. Nicholas' and St. John's were rung. He gave up the management of the theatre and about 1797 set out for a ten-year visit to America where it is stated he acted with success. He returned and in the Directory of 1811 is found to be one of the three dentists then in practice in Newcastle.

Newcastle has been extremely fortunate in the calibre of her medical historians and very little seems to have escaped Dr. Embleton, Professor G. H. Hume and Sir William Hume, Dr. Garnison, the late Professor Grey Turner and Professor F. C. Pybus. However, two small advertisements seem to have slipped past their notice with regard to the first resident surgeon and dentist in Newcastle, Frederick Horn. He was a surgeon in the Navy and

through the help of Admiral Osborne we now know that he served on the following ships:

Lynx from May 1, 1777 to May 6, 1778
Medway „ May 15, 1778 to June 4, 1780
Grafton „ June 6, 1780 to September 10, 1781
Crown „ March 17, 1782 to December 10, 1782

Dr. Embleton gave us the main information about him. He was appointed surgeon to the Royal Infirmary in 1800, took part in a celebrated discussion with Dr. Clark and Dr. Fenwick with regard to the fever wards, was a surgeon to the Dispensary and took an active part in the local Medical Society, of which he was the Vice-President for seven years and President in 1796. He contributed a number of papers to the Society and died in 1808 and was succeeded by his son in the appointment as surgeon to the Infirmary. In the Newcastle Directory for 1790 he is listed among the surgeons but in that of 1801 he describes himself as a surgeon and dentist. I was pleased to discover that he made the following announcement in December 1782:

"Frederick Horn takes this opportunity respectfully to acquaint the friends of his late uncle Mr. Henry Gibson that from some unavoidable circumstances (the ship of which he was surgeon being ordered to Gibralter and etc.,) he was prevented from addressing them sooner and soliciting the honour of their future favours in his professional capacity. As Mrs. Gibson is connected with him in the business he respectfully solicits the favours of her friends and flatters himself that his having attended the most eminent professors in London in the surgical and medical line and having been near six years a surgeon in H.M. Navy will have some weight in inducing those whom he has the honour to address and to give credit to his qualifications and assures them that his utmost abilities and attention shall be exerted to give satisfaction." In this interesting statement there is no mention of skill in dentistry and I wondered what type of a dentist he was. Imagine my delight when turning over the pages of the *Newcastle Courant* I found in the issue of July 29, 1786, the following:

"Frederick Horn, surgeon, acquaints the ladies and gentlemen of Newcastle and its neighbourhood that he has just returned from London where he has been completely instructed by an eminent practitioner in the business of a DENTIST. He scales and cleans and performs all the operations on the teeth, makes and fixes artificial and removes or prevents the irregularities which take place in the teeth of young people at the time of getting their second set."

The reference to the scope of Horn's work is of considerable interest to those of us who are dentists and of particular interest is the reference to children's teeth, as orthodontics is one of the most important branches of dental surgery to-day.

We find that a number of travelling dentists visited Newcastle. In 1761 Mr. Nathaniel Lee, an operator for the teeth, claims that he was present in Newcastle by the King's Authority.

"The famous Mrs. Bernard from Berlin and Brandenberg" who possessed "an infallible secret for cleansing the teeth and rendering them as white as alabaster notwithstanding they may be as black as coal remarkably done without use of an instrument." She was to be enquired of at the Half Moon entry in the Bigg Market. This was in 1773.

Mr. Marks, Jacob Hemet and Hemet Hart from Mannheim also stayed in Newcastle for a short while at different periods. I wonder if Jacob Hemet was a relation of George II's dentists—Peter Hemet senior, and Peter Hemet junior. In 1783 Mr. Crawcour, surgeon dentist, stayed for a short period and practised in Newgate Street. It is of considerable interest to us as this name is well known in dentistry because of the brothers Crawcour who early in the nineteenth century emigrated to America and started the row which is usually known as the Amalgam War. Was this man a relative—perhaps their father?

Messieur Le Sec, who was a pupil of Messieur Burdet, dentist to the Queen of France paid the first of a series of visits to Newcastle in 1790. Burdet was a famous dentist and it seems possible that Le Sec was a refugee from the Revolution.

There is a picture which shows Ruspini operating and through the window can be seen the lantern tower of St. Nicholas' Cathedral. There is no evidence that he visited Newcastle professionally but he married Elizabeth Ord, the daughter of one of the county families of Northumberland. The eighteenth century was remarkable for the travelling doctors, a number of these were eye specialists. One of the earliest of these travelling doctors to arrive in Newcastle was "Dr. Rayne, a Low German physician, who for the public good gives notice that he dexterously cures all sorts of deafness in young or old, whether it proceed from cold, relaxation of the drum, continual noise or imposthume in the ear or any other

obstruction in the auditory nerves to the advantage of a great number whom he has cured and restored to perfect hearing, several having been deaf for above 30 years who now hear as well as any person living. He performs the cure without any manner of pain and with such a safe operation as was never before performed".

In 1751, in January, "Mr. Turner, French surgeon and man-midwife who has studied at Paris all branches of surgery and has upwards of twelve years' practice in hospitals abroad, as appears by the testimonials granted him by Messieur Martinière, first surgeon to the King of France and lived some time in London and other parts of England where he practised the art of surgery with great success, takes the liberty now to acquaint the public that he treats the most inveterate wounds, ulcers and other sores of all kinds if they are not hereditary . . . he never undertakes a cure without taking, if it is required, a consultation with the established physicians and surgeons of the place, or from another place and is ready to perform before them all such chirurgical operations. He gives his advice and operates on the poor gratis. Inquire at Mr. Shackleton's in Pilgrim Street."

In 1758 there was the visit of Dr. Stalk, "occulist to the Royal Highness the Prince of Wales who lately restored several hundred to sight in Yorkshire such as have lost their sight or affected with any other disorder of the eye should apply to him at his lodgings."

Another ophthalmic specialist was Dr. Dove who came to Newcastle in the 1760s. Dr. Toscano, "the celebrated Danish physician", had an unfortunate quarrel with his interpreter when in Newcastle of which he gives full details in several public announcements.

The celebrated Dr. Graham visited Newcastle on several occasions and gave some of his usual spectacular performances, for instance in 1791 we find the announcement that "Dr. Graham and a young woman will give one more earth-bath exhibition this day Saturday July 9th, most positively for the last time from 12 noon to 6.0 o'clock in the evening in the large and commodious field at the side of Hanover Square, Newcastle in order emphatically to recommend this most natural, most safe and most radically efficacious practice to the world in general, especially to the country people". A week later he gave a similar demonstration in "Mr. Musgrove's garden to the left Without Westgate from 12 noon till 8 o'clock." "One woman who was scorbutic and one who suffered with leprosy and who baffled the physicians and surgeons in the Royal Infirmary in Edinburgh and in the Infirmary in Newcastle, and it is noted she stayed over fourteen months in each place without being cured, were publicly treated by the earth-bath method".

It is interesting that Mr. White, surgeon and man-midwife, No. 2 London House Yard North, the side of St. Paul's Churchyard, London, advertised in the Newcastle paper offering accommodation to pregnant ladies whose "situation requires a temporary retirement" and said that "they may be accommodated with apartments to lie in, agreeable to their circumstances and depend upon being treated with all attention and secrecy and their infants put out to nurse and humanely taken care of". The celebrated Chevalier Taylor was a frequent visitor to Newcastle where he gave himself great publicity.

As in most towns Newcastle had an open market place where stages were erected and upon which quack doctors were able to hold the attention of the crowd. There is a record of such a practitioner. "Dr Gibbons from London who keeps the public stages in Newcastle upon Tyne cures all sorts of agues, without giving the Jesuit's bark, in the space of 24 hours—no cure, no money. . . . He is the only noted man in the nation for this distemper and by reason the doctor's stay will be short. He advises all who have a mind to be cured to come before it is too late. He is to be spoken with at Mr. Rainton's in St. Nicholas Church Yard Newcastle." In a subsequent notice it says "he is to be spoke with at his chambers every market day near his stage".

I was amused to read in the *Courant* in 1761 "Wanted immediately a brisk active man to serve a travelling doctor as an Andrew. He must be a person of drollery and ready wit, if he has followed that calling before he will be the more acceptable, or if he plays an instrument. Like wise wanted a second-hand trumpet, cheap. Inquire of the printer of this paper. No letters answered unless post is paid."

The content of this paper lays me open to the charge of being a most biased type of historian. I have made no reference to Physicians such as Adam Askew, John Rotherham, John Hall, John Fenwick, John Clark—to mention only a few of the leading medical men who have not been included. How can I justify their omission? I have referred to Newcastle's fortune in the quality of her medical historians and as the physicians were men of distinction in the town practically all have been mentioned in some detail in the previous published works.

I am most grateful to Mr. Austin Hinton, Librarian to the Central Library, Newcastle, and to his assistants in the Reference Room, particularly Mr. Grimshaw and Mr. Muir.

[*February* 6, 1957]

Whither Medical History? [*Abstract*]

PRESIDENT'S ADDRESS

By DOUGLAS GUTHRIE, M.D., F.R.C.S.Ed., F.R.S.Ed.

DR. DOUGLAS GUTHRIE suggested that the time had come when the question "Whither Medical History?" might be asked with profit, even though it was impossible to supply an immediate answer.

It was interesting for the History of Medicine Section to look back to the date of its birth, when its founder, Sir William Osler, wrote to a friend in November 1912: "We have made an excellent start with our new Historical Section at the Royal Society of Medicine. There were over two hundred at the first meeting, so I hope it may be a success."

To-day, nearly half a century later, they might well pause to take stock of the situation. In this age of specialism, the art of medicine was in danger of being neglected, and this Section of a great Society, the only Section which was in no sense a specialty, and which still used a vocabulary intelligible to all, could play an important part in helping to counteract the somewhat narrowing effect of the present-day trend in medicine.

History provided an essential basis to medical education, and perhaps never before had there been so great a need for quiet retrospection, in order to look forward with clearer vision.

Moreover, there was a constant demand for fresh interpretations of historical facts to meet the varying outlook of each new generation of students.

Science had profited greatly from the specialist trend, but it could not supply all the answers to medical problems. There was still a subtle "something" which defied analysis, and it was not improbable that a closer study of the primitive attitude towards health and disease, the supernatural approach, might bring us nearer to the solution of problems which science alone could not solve.

There was also a need for a more philosophical approach to medicine, so that thought and reason might keep pace with observation and experiment. The time had come, too, for a re-statement of the Hippocratic oath in terms suited to modern conditions. Unfortunately this ancient and influential charter of medical conduct was almost wholly neglected in English medical schools, although in all four Scottish universities it formed an important item in the ceremony of medical graduation.

Dr. Guthrie also discussed the need for more widespread teaching of the history of medicine. A short course of 6 or 8 lectures, giving an outline of the main trends of medical thought, and an account of the leading pioneers, sufficed to interest the student, who might then continue to explore this exciting field for himself. Some account of the history of the particular medical school ought to be included, and due tribute should be paid to the importance of medical ethics. The history of each of the various branches of medicine was best included within the subject rather than in any separate lectures. One historical lecture might suffice, and it ought not to be an introductory lecture, being best deferred until the student already knew at least part of the subject, and could therefore appreciate an account of its history. Lectures were not the only means of approach to history. Exhibits of books, manuscripts, photographs, instruments and apparatus should be available, clearly and amply labelled. Societies devoted to medical history should include among their members librarians, chemists, nurses, dental surgeons, and indeed all who might be interested. There ought also to be a close link with general historians, of whose studies medical history is simply one aspect.

The wide appeal of medical history was one of its main attractions, in this age of centrifugal specialism. It was a valuable means of bringing together again all the various specialists, and was, perhaps, the best method of retaining the interest of the entire profession in that attitude towards medicine which, since the days of Hippocrates, has been so aptly termed "The Art".

Section of Surgery

President—Eric A. Crook, M.A., M.Ch., F.R.C.S.

[*January* 2, 1957]

Non-specific Conditions of the Large Intestine

PRESIDENT'S ADDRESS [*Abridged*]

By Eric A. Crook, M.A., M.Ch., F.R.C.S.

It is my intention in this Address to consider certain problems that are not yet fully solved in connexion with diseases affecting the lower reaches of the alimentary tract. Two problems in particular have provided interest in recent months—that of the ætiology of ulcerative colitis and that of the pathological processes that take place in lymphogranuloma venereum as it affects the rectum and the lower colon.

Lack of knowledge of the cause of a disease must, of necessity, place its treatment on an empirical basis. Certain diseases of the colon are in this category and the treatment has to depend on general measures to deal with the processes that are taking place, or, alternatively, on removal of part or the whole of the organ, leaving the patient at a physiological disadvantage. Idiopathic or ulcerative colitis is one of these conditions.

This name was first given by Wilkes and Moxon in 1875 after a study of colons from patients who had suffered from long-standing or recurrent diarrhœa. Many diseases were included that have subsequently been shown to have a separate cause and so have become separate entities, such as dysentery, typhoid and tuberculous ulceration, and, more recently, Crohn's disease and lymphogranuloma.

The ulcerative colitis that is now left after these separations is considered to be a disease entity, though the difference in the types of clinical picture presented suggests that it may, even now, comprise several different diseases. The common form starts in the left side of the colon and tends to extend both proximally and distally. A right-sided form occurs occasionally, being only one-tenth as common as that on the left. This is considered by Brian Brooke to be a different disease, in view of its tendency to involve the lower ileum and because of its liability to recur at a higher level if it is treated by ileostomy. Brooke further considers that a form of granular proctitis, that is occasionally observed and has little or no tendency to spread to the colon above, is also a different disease.

Crohn's disease and lymphogranuloma, though now usually considered separate and distinct from ulcerative colitis, have many points of similarity. Crohn, in 1932 in his original description of ileitis, showed the pathology to be different in the disease he described from that found in "right-sided ulcerative colitis". He described the clinical picture and the tissue changes that take place.

George Lumb in 1951 gave an account of the pathological changes that are found in Crohn's disease and ulcerative colitis and considered there was great similarity between the two. He stated "we appear to be dealing with a non-specific inflammatory lesion, indistinguishable from other inflammatory lesions", the changes being (i) thickening of the bowel-wall, (ii) narrowing of the lumen, (iii) lumpy mucosa (cobblestone appearance when the ileum is involved, pseudo-polyposis when the colon is affected), (iv) infection around the bowel.

Brooke (1954) in his treatise on ulcerative colitis considers the pathological changes in the colon, when ulceration occurs in association with Crohn's ileitis, to be different from those found in ulcerative colitis. Bensaude and Lambling of Paris showed in 1936 that certain inflammatory diseases of the rectum were due to the virus of lymphogranuloma venereum. The uncertain state of our knowledge of the ætiology of Crohn's disease and of ulcerative

colitis and the doubts about the mode of involvement of the rectum by the virus of lymphogranuloma have suggested the comparison that I propose to make between these three conditions.

This comparison is made from five aspects: (i) the incidence of the condition; (ii) the course it takes; (iii) the pathological changes found in the disease; (iv) the possible causes; and (v) the response to treatment.

(i) *Incidence*

In Crohn's disease we find the majority of cases occur between the ages of 20 and 30 and especially at the earlier part of this period. There is a slight preponderance of males over females and there are instances reported where more than one member of a family has been affected. Crohn quotes many instances of this in his early series. All classes of society are affected equally in ileitis and race and climate have no influence. The temperament may be highly-strung and anxious in some cases but the personality of the patient suffering from Crohn's disease is more stable than is the case in ulcerative colitis.

In ulcerative colitis the main incidence is between 20 and 40 years of age. There is a definite preponderance of females. In a recent review of cases made by Ian Macdougall at the Gordon Hospital this is 1·5 female to 1 male. Sedentary workers are more frequently affected than those who do manual work. The condition is more common in those of higher educational standard. In certain communities that are composed mainly of the poorer classes the condition is rare. At the City Hospital, Boston, U.S.A., a hospital of some 2,000 beds and serving the poorer part of the city, I found that ulcerative colitis was considered to be a rare disease. It is interesting to note that in Jamaica the disease is almost unheard of, the occasional case that does occur being usually in the white population of the island which constitutes less than 5%. Sufferers, for the most part, have rather unusual or abnormal personalities. They are inclined to be weak and dependent on others. Many of them are over-conscientious and sensitive, having a shy and timid disposition. They have a highly-strung and tense temperament. The onset of the disease or of its exacerbations is often precipitated by a superimposed emotional disturbance.

In lymphogranuloma affecting the rectum and colon, the incidence is limited almost entirely to the female. This is probably explained by anatomical factors, to be discussed later. The disease does not occur in the British Isles except for the occasional case in the larger ports and it is found mainly in the negro races. It is very common in Jamaica in the form limited to the genital tract and also that involving the rectum. In the U.S.A., series of cases are reported and it is found to occur twice as commonly in negro as in white people. The disease is reported in France but is relatively rare.

In comparing the incidence of the three diseases we find differences of susceptibility in each. In Crohn's disease there is some hereditary predisposition, in that several members of a family may be found to suffer. In ulcerative colitis personality and temperament show some peculiarity in most cases. In lymphogranuloma, racial differences determine the liability of occurrence. There is therefore a different background in each of the three diseases.

(ii) *The Course*

In considering the course that the three diseases follow we recognize that Crohn's disease may be found in an acute or a chronic form. The acute form presents a clinical picture similar to that of appendicitis, but differing in having associated diarrhœa. Some of these cases, rather less than half, settle down and finally resolve completely. The others fail to clear up and pass on to the chronic form of the disease. The onset of Crohn's disease is in most cases gradual, and the significance of the early symptoms of periodic attacks of diarrhœa and general weakness is not appreciated by the patient. The diarrhœa is not so profound as in ulcerative colitis. The early symptoms are often present for two or three years before they are recognized as being due to Crohn's disease. The infective lesions in the rectum and surrounding tissues may appear at this early stage and call attention to the significance of the diarrhœa. They are a special feature of Crohn's disease and not simply caused by the diarrhœa. They start as a surface infection, often in a crypt of Morgagni and from this infection escapes through the bowel wall and causes a perirectal abscess, which in its turn gives rise to a fistula. The stool is watery, and contains no visible mucus or blood. A series of cases that I reported in a paper read to the Royal Society of Medicine in 1935 showed, however, that anæmia due to blood loss may be an early feature of the disease. Abscess formation near the infected ileum and subsequent fistulæ are frequently found, the latter opening on the abdominal wall—especially if there has been a previous appendectomy—or into another portion of the bowel or the bladder. Symptoms of intestinal obstruction are liable to develop at a later date. Crohn's disease is usually progressive in

its course, advancing rapidly in some cases, slowly in others and sometimes remaining localized in the terminal ileum for many years.

The course taken by ulcerative colitis is rather more varied. The onset is usually more acute and is followed by periodic attacks of varying severity and length. In some cases the first attacks are mild, becoming later more severe and more frequent, until the symptoms become continuous with periodic exacerbations, the essential features of the attack being abdominal pain and diarrhœa in which blood and mucus are passed. Anæmia is a constant finding, but abscesses and fistulæ do not occur except in the perianal region. The disease has a long course. Intestinal obstruction seldom develops.

In lymphogranuloma a spurious diarrhœa is found in the early stages. Blood and mucus are passed and the fæcal material is solid. Abscesses and fistulæ often occur. Obstruction due to stricture formation is a constant feature.

In the course followed by the three diseases the early stages are marked by the presence of diarrhœa, attributable to irritation of the surface layers of the bowel, the character of the diarrhœa varying with the region involved. In Crohn's disease and ulcerative colitis the onset may be acute, passing into the clinical form in which the disease is most often observed. Recurrent attacks with intervals of freedom may continue for years but eventually the symptoms become continuous, presenting periodic exacerbations. Ulcerative colitis in its behaviour tends to be more capricious than Crohn's disease, some attacks being more violent than others, and in some cases unexpected rapid improvement takes place. In general, both diseases are relentless in their course, very few cases clear up under treatment; in some, advance is prevented, but in the majority operative treatment, removing the affected bowel, is necessary.

In lymphogranuloma the earlier course of the disease has not been so fully studied. The rectal manifestations are an extension of the primary disease in the genital tract with the possible exception of the occasional case which occurs in the male. The course, however, is similar to that of the other two. Recurrent attacks occur over a period of many years and obstructive symptoms are gradually added to the picture.

(iii) *The Pathological Changes*

In comparing the pathological changes, we find in Crohn's disease an inflammation of the mucosa and submucosa—with or without ulceration—swelling and proliferation of lymphatic endothelium in both the intestine and the lymph glands—with occlusion of lymphatics and resultant œdema. The changes cause a generalized thickening of all coats of the bowel with a boggy mesentery and enlarged lymphatic glands. The bowel becomes a solid tube and a fibrinous exudate forms on its serous surface. Adjacent coils become adherent and a tangle of bowel, matted together, is formed round the coil that is primarily involved. These adhesions are followed by escape of infected material and abscesses form between the coils with subsequent internal fistulæ. Advancing changes also take place in the mucosa of the bowel. In patches denuded by the ulceration the mucous membrane is replaced by scar tissue covered in part by a modified columnar epithelium. Islands of mucosa that are left become œdematous and present a "cobblestone" appearance. These changes may be limited to one region which is most frequently the terminal ileum but "skip lesions" are found at a distance above or below with intervening healthy "skipped areas". Hadfield (1939) describes the histological appearances as those of submucosal-coat thickening with lymphatic tissue showing well-defined non-caseating giant-cell systems, free from acid-fast organisms. Similar changes are found in the regional lymphatic glands. There is associated obstructive lymphœdema. This, in the course of time, is replaced by fibrous tissue which tends to contract and to result in stricture formation. In ulcerative colitis the earliest changes are found in the mucosa which becomes swollen and red with a tendency to bleed when touched by the examining sigmoidoscope. In some cases no ulceration is visible, in others multiple shallow ulcers may be seen. These changes can usually be recognized but proof of the condition and an indication of further disease in the colon above can be obtained by biopsy of the rectal mucosa. It has been the practice at the Gordon Hospital to study these cases by taking a fragment of tissue for section at 11 cm. from the anal orifice. There is no special reason for selecting this level for the biopsy other than the advantage of having a fixed point in the bowel so that comparisons can be made more accurately. George Lumb has shown that characteristic changes of ulcerative colitis are shown by the special inflammatory process and the alteration in the architecture of the mucous membrane. The ulcers in the colon extend and the mucosa becomes undermined and partially destroyed. Remnants of surviving mucosa stand out as tags and, becoming œdematous, have the appearance of polypi—a state of pseudopolyposis. This stage may be reached before any change is visible in the external appearance of the bowel as seen at laparotomy. The process gradually penetrates more deeply through the muscle wall producing a state of thickening and of hyperæmia of the serous coat. There is no tendency for adhesions to neighbouring

coils of bowel to take place and fistula formation does not occur. The enlargement of para-colic lymph glands is only slight. Areas in the bowel lumen that have been denuded of mucosa become covered with a typical epithelium and scarring takes place in their base. A rigid narrow state of the bowel may result but true stricture formation is unusual though it sometimes takes place at the recto-sigmoid junction. The histological changes described are submucosal œdema, mucosal hyperplasia, necrosis and ulceration, associated with diffuse round-cell infiltration including eosinophils and, in the later stages, advancing fibrosis. The picture is one of a pathological state rather than a specific process.

In lymphogranuloma when it affects the rectum, the earliest changes are seen in the mucous and submucous tissues. These changes may be limited to the lower part of the rectum but in many cases they extend to the upper rectum and the pelvic colon. Cases are reported where the disease has been found as high up as the cæcum. These lesions, when they occur in the colon, are separated from the main disease by stretches of healthy bowel. In the barium enema X-ray, a saw-tooth pattern, indicating spasm, is shown in the early stages similar to that seen in ulcerative colitis. A granular proctitis is present with a swollen and congested mucosa and superficial ulceration with a blood-stained muco-purulent discharge. Lymphatic œdema is found in the outer layers of the rectal wall and perirectal cellular tissue, causing an appearance of elephantiasis and tag formation round the anal orifice. Suppuration in the cellular tissues occurs and, after the bursting of the abscesses, fistulæ are found with openings in the perianal skin. In the female a recto-vaginal fistula may be found. Narrowing of the rectum is produced by œdema in the wall and later by fibrous tissue which results in a tubular stricture 3 in. or more in length. The X-ray appearance is then very similar to that of the "string" sign seen in Crohn's disease. No appreciable enlargement of the regional lymph glands is found at laparotomy at this stage—a feature that is characteristic of the genital manifestations of the disease. The histological appearances of the tissues are described as those of an intense non-specific granulomatous inflammatory process. The cellular tissue is infiltrated with leucocytes and plasma cells and in places there are collections of endothelial and giant cells surrounded by lymphocytes and numerous plasma cells. Lymphatics are dilated and contain lymphocytes and plasma cells and an increasing amount of fibrous tissue is found. In two cases of lymphogranuloma reported by Hawe (1951) the following changes were found: "Non-specific inflammatory reaction. Cellular infiltration of plasma cells, monocytes and polymorphs, with accompanying fibroblastic reaction, some foci of epithelioid cells resembling tuberculous systems but without caseation. Changes extend through all coats of the gut with maximum intensity in the submucous layer."

So in the pathological changes we find great similarity in the three diseases. Lumb (1951) considers the resemblance between Crohn's disease and ulcerative colitis to be so close that they may be the same disease. In the later stages of the pathological processes, however, definite differences do appear but the tissue changes of Crohn's disease and those of lymphogranuloma come to resemble each other more closely. It would seem that the pathological evidence puts Crohn's disease and lymphogranuloma together and that ulcerative colitis cannot be linked directly with either.

(iv) *The Possible Causes*

In considering the possibility of a common cause for the three conditions we find that in Crohn's disease the ætiology has not yet been fully explained. Search has been made for a specific organism but none has been found. At the Mayo Clinic in 1938 a series of cultures was taken from specimens and lymph glands in the operating theatre and many organisms were grown but the findings were not constant. Dysentery organisms were not found. The presence in the microscopic section of giant cells that are proved not to be tuberculous in origin has suggested that certain small irritating food particles, acting as "foreign bodies" may be a causative factor. A virus has been suggested as a cause in view of the similarity between the tissue changes in Crohn's disease and lymphogranuloma in which latter the association with a virus has been established. If the ætiology were the same, however it would seem probable that the two conditions would occur together at times. This has not been recorded; Frei's test has proved to be negative in ileitis. However, some other virus may be responsible. The behaviour of ileitis in its tendency to spread and its liability to recur after resection does seem to point to some infective cause and we have ruled out bacteria as a possibility. It has been suggested by Chess and others in 1950 that some mechanical irritation of the mucosa of the ileum may be the cause. In experimental work on dogs, the giving of sand by mouth has produced ileitis, but in human beings no association has been found between the ingestion of irritants and the development of ileitis. Trauma, with interference of the blood supply of the ileum and resulting pathological changes in the tissues, has been suggested but there is no support for this theory. The frequent sequel of appendicectomy and ileitis has suggested an association between the two. A recent operation at

which the appendix was difficult to find and even more difficult to remove was followed by recognizable Crohn's disease a few months later. The trauma involved at the operation may have been a factor in causing the latter, but it seems more likely that ileitis was present at the time of the operation but had not reached a recognizable stage. We recognize the close similarity between the clinical pictures of acute appendicitis and the acute form of Crohn's disease. Enlargement of the regional lymph glands is a constant feature of terminal ileitis and it has been suggested that lymphatic block may constitute the initial process which leads to lymphatic œdema in the mesentery and wall of the terminal ileum with subsequent inflammatory changes. Experimental blocking of lymphatics in animals has resulted in thickening of the bowel wall. This does not, however, prove that the changes proceed in this direction in the human body.

The ætiology of ulcerative colitis is also a mystery. In its acute stage the disease is indistinguishable from bacillary dysentery, both clinically and pathologically, and is only dissociated by bacterial evidence of the latter. It is, however, possible that an attack of bacillary dystentery may be the onset of ulcerative colitis and that the tissue changes of the latter are kept alive by organisms that normally inhabit the bowel after the dysentery bacilli have disappeared. The association of a diplostreptococcus described by Bargen in 1924 has not been confirmed by later workers and the theory has been abandoned. Vitamin deficiency has been blamed but is not present until the later stages of the disease when it is more likely to be the result rather than the cause and is attributable to the reduced diet and the rapid passage of food through the bowel. In 1933 Florey wrote on "the function of mucus and the early stages of bacterial invasion of the intestinal mucosa", and in 1949 Meyer and others described an enzyme "lysozyme" that had power to destroy mucus and was present in high concentrations in the bowel content in ulcerative colitis. He suggested that the enzyme destroyed the mucus and so removed the natural protection of the cells of the bowel, exposing them to digestion by normal proteolytic enzymes and to infection by normal bowel organisms. This mucolytic enzyme is not present in normal stools. Its high concentration in ulcerative colitis has been considered by Sammons (1951) to be the result of lysis of the pus cells that are present, being therefore the result of the secondary infection of the bowel wall and not the cause. The possibility of an allergy has been considered. Sigmoidoscopy carried out as a routine in minor bowel disturbances shows at times a patchy condition of the mucosa with raised vascular areas and small papules—a state suggestive of urticaria of the skin. This theory seems unlikely, as sufferers from ulcerative colitis are not as a rule subject to allergic conditions. The emotional instability that is often associated with the onset of ulcerative colitis and the known effect of the emotions on alimentary function have suggested a search for a neurological cause of the disease. Wright *et al.* in 1938 described the effect of stimulating the sacral division of the parasympathetic nerves, the nervi erigentes, in cats, thereby producing increased muscular activity and secretion of mucus. In dogs, long-continued stimulation by various methods including cholinergic drugs, has been shown to lead to colonic engorgement, hæmorrhage and ulceration, which may prepare the way for further injury and secondary infection. Can we consider the local reaction of the colon in ulcerative colitis to be the result of long-continued overstimulation of the parasympathetic nerves, particularly the sacral outflow which supplies the distal colon and rectum?

The ætiology of lymphogranuloma is on a firmer footing. Bensaude and Lambling (1936) described their investigations of proctitis, especially when associated with stricture formation. They had found that lymphogranuloma was a frequent cause, the specific intradermal test that had been introduced by Frei in 1925 being positive and also the complement-fixation test. This established a recognized rectal lesion as a granulomatous state produced by a known virus. The virus of lymphogranuloma had been isolated by Hellerström in 1930. Bensaude and Lambling expressed the view that the virus reached the rectum from the genital tract via pelvic and perirectal lymphatics, claiming that the disease affected the outer layers of the rectal wall before it reached the mucosa. Hawe (1951) considered that in the female the infection reached the rectum from the vagina by the perirectal lymphatics, whereas in the male the rectum was involved by direct inoculation of the anal mucosa. Roger Miles has recently carried out a large-scale investigation of lymphogranuloma in University College of the West Indies, Jamaica and has shown that in a large proportion, possibly all, of the cases of rectal involvement the infection has started on the mucosal surface of the bowel. He considers that in the female, the rectum is infected by spill from the vagina. In the male, in whom the rectal manifestations of lymphogranuloma are much less frequent, the rectum is probably involved primarily by direct implantation of the infection on the mucosa. The cause of Crohn's disease and of ulcerative colitis is still undiscovered but that of lymphogranuloma is known. The similarity of tissue changes in Crohn's disease and lymphogranuloma suggests that the former may be due to a virus infection though not the specific virus established as the cause of lymphogranuloma.

(v) *Response to Treatment*

In considering the response to treatment it is found that Crohn's disease and ulcerative colitis behave in much the same way. Fundamental principles in treatment form the mainstay—rest and a diet high in protein, vitamins and calories and low in residue with plenty of fluid. The insoluble sulphonamides sulphasuxidine and sulfathalidine have a place in controlling secondary infection. Of the antibiotics, chloramphenicol and aureomycin are used, the latter having a wider range of action and usually giving some improvement and, occasionally, a complete remission. They have, however, no curative effect on the established disease.

In lymphogranuloma venereum, Roger Miles describes a series of cases treated, some with chloromycetin, some with erythromycin and others with aureomycin and with each drug, rapid improvement was obtained. Pain and tenesmus disappeared, blood and mucus cleared up and the sigmoidoscope showed definite improvement in the state of the mucosa. These cases were followed up and in over 70% of patients treated, great improvement or complete cure was obtained.

As surgical measures are often necessary, their effects should be considered. In Crohn's disease a by-pass for the intestinal contents by ileo-transverse colostomy has been abandoned in favour of a resection of the affected bowel. Resting the diseased area led to healing in some, but not all, cases. In ulcerative colitis the establishment of an ileostomy gives immediate benefit but subsequent removal of the colon is necessary to obtain a cure. In cases where the rectum is appreciably involved this organ must be removed as well. The need for this has been shown by Brooke in a case where arthritic symptoms were associated with the original disease, removal of the colon as far as the rectum did not cure the joints but this cure was obtained by a subsequent removal of the affected rectal stump. In cases where the rectum is not extensively involved, Aylett (1956) at the Gordon Hospital has shown that ileorectal anastomosis after excision of the colon gives good results and no trouble from the retained rectum follows. In lymphogranuloma venereum it has been stated above that antibiotics give good results in the earlier stages when the disease is limited to the mucous and submucous coats of the rectum. This treatment can be combined with gentle dilatation of the bowel in the early stages of narrowing, but surgical resection is necessary when a definite stricture has developed or infection has spread to the perianal tissues with abscess or fistula formation. The mere establishment of an iliac colostomy above the diseased area without resection of the latter is useless.

All three diseases responded to the insoluble chemotherapeutic drugs in variable degrees. The effect produced seems to be due to the action of these drugs on the secondary infection present; they have no curative effect. Surgical measures adopted to rest the diseased bowel by diverting the contents relieve but do not cure; excision of all the diseased tissue is necessary for this, otherwise there may be a recurrence. A "skip lesion" in Crohn's disease and in lymphogranuloma may have escaped notice or, in ulcerative colitis, the colon may have been involved beyond the point visible to the naked eye.

General Comparison

The similarity of the early stages of all 3 diseases suggests that they may be one and the same disease. The special features in each may be explained by the local differences in the region of the bowel involved, modified by idiosyncrasies of the patient and differences in race and climate. As the disease progresses, however, though Crohn's disease and lymphogranuloma maintain many parallel features ulcerative colitis becomes more like a separate disease: the underlying process does not behave like an infection as appears to be the case in Crohn's disease and lymphogranuloma. In the latter an infection has been shown to be the cause and it may well turn out to be the explanation of the former.

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Section of Obstetrics and Gynæcology

President—R. A. BREWS, M.D., M.S., F.R.C.S., F.R.C.O.G.

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DISCUSSION ON DYSMENORRHŒA AND UNEXPLAINED PELVIC PAIN

Mr. Wilfrid Mills: *Dysmenorrhœa*

Dysmenorrhœa still presents a fascinating problem. Despite investigation of intra-uterine pressure with balloons (Moir, 1934) and uterine blood-flow with radioisotopes (Flick *et al.*, 1956) it remains largely unsolved. There is no final agreement on the pathway of sensory nerves from the uterus nor the reason for uterine pain being referred to so many different areas of the skin. We cannot even say how far the pain is caused by spasm of uterine muscle or by ischæmia from inadequate blood supply. It has been suggested that it may be associated with organic disease of the sympathetic ganglion cells (Davis, 1938), of the ovary (Browne, 1949) or even of the ureter (Read, 1951). There is often a suggestion of emotional immaturity about these patients and this is perhaps borne out by the finding of a tight hymen precluding pelvic examination far more often than in girls of an equivalent age group with menorrhagia.

The extent of this disorder is considerable and it seems to vary widely between social classes and nations. A figure of 16% has been quoted from among British nurses (Bishop, 1950). The number of cases seen by any gynæcologist will depend partly upon his reputation for sympathetic interest and his success in the past, but also upon the skill and self-reliance of the practitioners whom he serves. It is difficult to get any unselected series for most specialists see only the few resistant cases.

Attitudes towards treatment are most variable. Some gynæcologists prescribe only simple measures and consider the whole problem to be over-rated, regardless of nuisance to industry when young women are principally employed and require regular days off. Others observe that dysmenorrhœa is seldom seen among well-adjusted, sexually adequate and psycho-somatically sufficient women (Hamblen, 1945) and regard the problem as purely one for the psychiatrist. Perhaps they fail to appreciate the emotionally demoralizing effect of regular, severe and anticipated pelvic pain with its concomitant social disorganization. Others, more properly described as gynæcological surgeons, practise complicated ways of interrupting the alleged sensory sympathetic nerve pathways and persuade patients that a surgical operation is a small price to pay for the chance of a permanent cure. Those who understand the nature and action of steroid hormones feel that a solution should be well within their compass and in fact these hormones do give great relief to many patients. However, the family doctor probably cures or relieves far more of these sufferers than we realize by means of a multitude of relatively simple preparations. His knowledge of the upbringing and background of the patient together with her reaction to pain on previous occasions enables him to assess her far more competently than the gynæcologist meeting her for the first time.

I have done no research nor have I followed up a long series of cases treated identically in this condition. I have, however, recorded what my patients have told me and as this is a symptomatic condition the patient is surely the best judge of the results.

I shall deal only with that common type of dysmenorrhœa without demonstrable pelvic disease; it may start at puberty or some few years later but there should be no complaint of pain apart from the first few days of the menstrual loss. The patients are commonly unmarried and in their late 'teens or early twenties. Physical examination often shows unusual tightness of the ring of the hymen with sometimes hypoplasia of the vulva and vagina but there are generally no other abnormal findings.

Temporary relief or permanent cure may follow a great variety of therapeutic and other incidents and although the connexion may well be fortuitous it is tempting to believe in a causal relationship. I have listed some of these incidents and forms of treatment which, in my own experience, have been judged successful by the patient herself, after a reasonable interval of time (Table I).

It is also instructive to consider those occasions, fortunately less common, on which the patient is convinced that some incident or form of treatment has been responsible for significant deterioration in her condition (Table II).

It is easy to be sceptical as to the value of treatment in a condition where relapse is so common. But I have found a decided reluctance among these patients to express satisfaction unless relief has been obtained. The following cases illustrate some of these points.

TABLE I.—CONDITIONS CURING OR IMPROVING DYSMENORRHŒA

1. The passage of time
2. Marriage
3. Pregnancy (sometimes abortion)
4. Education and simple psychotherapy
5. Attention to bowel and physical exercise
6. Atropine and similar drugs
7. Peripheral antispasmodics (e.g. Priscol)
8. Œstrogen to inhibit ovulation
9. Œstrogen following ovulation
10. Androgens
11. Dilatation and other trauma to the cervix
12. Presacral pelvic neurectomy

TABLE II.—CONDITIONS AGGRAVATING DYSMENORRHŒA

1. Change of residence or occupation
2. Marriage, especially if infertile or unhappy
3. Abortion
4. Progesterone
5. Œstrogen inadequate to inhibit ovulation
6. Trachelorrhaphy

ILLUSTRATIVE CASES

I. Mrs. A. had already been treated elsewhere successively by D. and C., Gilliam suspension and then a second D. & C. but her dysmenorrhœa was still severe. Confidence was restored by inhibition of ovulation with œstrogen and the relief continued. Then a sequence of 3 abortions (2 being at 18 weeks) called attention to the incompetent cervix which was repaired by trachelorrhaphy. Her dysmenorrhœa immediately became intense and hysterectomy was demanded. Fortunately she was then cured by carrying a pregnancy to term.

II. Miss B., a trained nurse, had had little relief from analgesic drugs and was advised to inhibit ovulation with œstrogen. In the first month the dosage was inadequate, the period started during the course of treatment and the pain was more intense and prostrating than ever before, requiring morphine for relief. Subsequent correction of dosage was satisfactory and pain was fully relieved.

III. Mrs. C. was first seen aged 17. Her dysmenorrhœa was completely relieved by œstrogen from the seventeenth day until the onset of the period and the relief persisted after treatment had been discontinued. Subsequently she relapsed slightly but required no further treatment or advice until the pain returned, following an abortion soon after she was married.

IV. Mrs. D. had a bad family history of dysmenorrhœa and obtained no relief in her youth. She married and was advised to have a family but each of her two confinements brought trivial improvement that lasted only a few months. At 35 she welcomed hysterectomy as her monthly prostration interfered with her hunting appointments.

V. Mrs. E., an exceptionally gifted and intelligent woman, suffered a severe disorder of uterine action at her first confinement. On being questioned about dysmenorrhœa, she replied: "My dysmenorrhœa disappeared as soon as I heard a psychiatrist say that it was always emotional; it never returned."

Discussion.—The conclusion must surely be that there are many different causes for and different mechanism involved in the production of this common symptom, and that each patient requires individual assessment.

As a working hypothesis I try to fit my patients into one of six categories (Table III) and

TABLE III.—CLASSIFICATION OF PRIMARY DYSMENORRHŒA

1. Deficient uterine blood supply
2. Stenosis of cervix
3. Excessive luteinization
4. Pelvic congestion
5. Excessive innervation
6. Emotional factors

to treat them accordingly. Although the initial assessment may have to be modified later the classification works well in practice. Sometimes more than one factor may be operative. It is easy to imagine an avascular uterus which responds to marriage, pregnancy and œstrogen. The concept of a tight cervix is strengthened by the familiar experience that the difficult dilatation is subsequently the most successful. The idea of excessive progesterone producing a modified decidua has long been held to explain membranous dysmenorrhœa (Whitehouse, 1935) and to give a rational explanation for therapy with premenstrual œstrogen. The picture of uterine congestion is less easy to visualize but at least it would explain the success that may follow physical exercise, peripheral vasodilators and purgation in drawing blood away from the pelvic organs. The uterus that is too liberally endowed with sensory nerve endings is demonstrated in the patient who cannot endure a simple cauterization of the endocervix and who may require a sympathectomy operation; emotional and neurotic patients are familiar to us all.

In consultant practice some of these categories can often be excluded by the failure of treatment that has already been given, but there may be a secondary emotional imbalance due to frustration with the apparent incurability of the pain. The first prescription may in some cases be the inhibition of ovulation by œstrogen in order to restore the confidence of the patient in medical advice. This, if continued for several months, will sometimes produce so much permanent relief that further therapy is unnecessary, but otherwise there will now be ample co-operation from the patient in evaluation of other measures according to her probable classification. Patients with congestion have been cured, apparently permanently

by three or four months on testosterone; others have responded unexpectedly well to œstrogen given subsequent to ovulation. Dilatation of the cervix is used more freely in the married woman especially if infertile, but presacral neurectomy is very seldom employed by me as a formal procedure on its own.

Conclusion.—Since adopting the principle that primary dysmenorrhœa may be a symptom of several different uterine disorders, a classification has been evolved to satisfy the available evidence and to provide treatment on an individual basis. One of the results has been that these cases are now welcomed in the gynæcological department.

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Mr. Wilfrid Mills: *Unexplained Pelvic Pain* [*Abstract*]

The problem of pelvic pain is one of diagnosis and ancillary methods were discussed. A personal series of 100 cases of pelvic pain shows a preponderance of young married women with family limitation. The final diagnosis will often depend upon the response to different forms of conservative treatment. Almost half of the patients have been considered as "functional" rather than "organic". Most cases obtain relief eventually if conservative forms of treatment are combined with attention to social factors. Radical surgery gives consistently good results.

Mr. Albert Davis: *Surgical Treatment*

In the absence of gross pathology the surgery for pelvic pain resolves itself into one or other of the several forms of sympathectomy. These range from simple stretching of nerve fibres to actual sympathectomy, and will be described seriatim in order of their severity.

Dilatation of the cervix.—This is, interestingly enough, the original sympathectomy, for it owes its results to rupture of the sympathetic plexus in the cervix itself. I described this plexus (Davis, A., 1933, *J. Obstet. Gynæc. Brit. Emp.*, **40**, 481) some twenty years ago and since then we have been able to trace its connexion with the main pelvic plexus of Lee Frankenhauser. It lies just beneath the epithelium surrounding the external os, and I have called it the "sub-epithelial plexus of the tip". It is the rupture of this plexus which is responsible for the relief of the pain in dysmenorrhœa, a logical explanation which disposes of our previous uneasy belief in the obstructive and angulation theories. To produce effective rupture of this plexus it is obviously necessary to tear the cervix. The nulliparous cervix ruptures as a rule after dilatation to No. 8 Hegar—it is a common finding to note how suddenly dilatation becomes easier at this stage, the larger dilators passing very easily afterwards. It is, of course, obvious that the laceration so produced should be controlled, and this is best accomplished by the use of graduated dilators (Fig. 1). The one illustrated is slightly

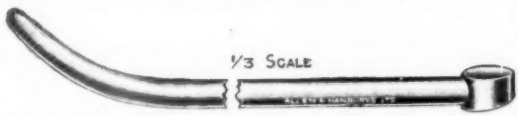


FIG. 1.—The author's graduated-stem uterine dilator.

graduated for about 3 in. from the tip, and each one passes through three sizes, 3–6, 4–7, &c. With this method approximately 30% of all cases of primary spasmodic dysmenorrhœa are cured, or adequately relieved.

Alcohol injection.—The rationale here is to destroy the uterine afferent nerves where they are most closely concentrated, i.e. in the pelvic plexus of Lee Frankenhauser. This lies at the side and in front of the ampulla of the rectum on either side, being formed by the fusion of the hypogastric plexus and the nervi erigentes from the middle three sacral nerves. The technique is to pass a needle into the plexus from the vagina. With the patient in the lithotomy position the cervix is seized with vulsella and retracted towards the left. The right fornix is further exposed with the aid of a flat lateral retractor. A long, graduated galserian needle is then passed horizontally through the vaginal mucosa at the side of the cervix for a distance of 0·5 cm., and the retractor removed. The needle is now passed backwards and outwards for approximately 1·5 cm., at an angle of 45 degrees to both the sagittal and coronal planes, and guided by a finger in the rectum to a point 0·5 cm. from the

side of the rectal ampulla. The needle is then withdrawn for 0·5 cm., and 1 c.c. of 95% alcohol injected, the needle point being kept slightly but continually moving. The same procedure is then repeated on the other side.

Bios and Young infiltrate the whole of the parametrium by injecting 8 c.c. of alcohol on each side of the cervix and body of the uterus. Their method owes its success to destruction of the most peripheral uterine branches of the pelvic plexus, and it seems more reasonable to alcoholize that structure directly in the manner just described, for the quantity of alcohol necessary is very considerably less. I have lately, however, combined the two methods by first injecting the plexus, and then placing 1 c.c. of alcohol in the parametrium close by the side of the uterus, so as to block any accessory nerve-fibres.

Perforation of the rectum with consequent cellular infection is avoided by making the injection 0·5 cm. away from that organ, as calculated from the internal finger. Injury to the ureter is prevented by adherence to the technique described, which keeps the needle point lateral to it. The uterine artery, if touched, usually slips away from the needle, but constant movement of the latter is a further safeguard.

Hofstatter has suggested that the injection of a destructive substance like alcohol into the loose pelvic cellular tissue might cause a local aseptic necrosis. I have not encountered this complication, and experience with alcohol injection elsewhere leads one to regard it as only a very remote possibility.

It is unnecessary to use more than 1 c.c. of alcohol on each side, for only a partial destruction of the plexus is aimed at. The upper part of the plexus contains the motor nerves to the bladder, which have been shown by Learmonth to be indispensable to the proper function of that organ. With the quantity of alcohol suggested these fibres escape injury, but it is conceivable that larger amounts might damage them, with consequent urinary disorder.

The results on the whole are relatively good, about 60% of cases of dysmenorrhœa being cured.

Presacral neurectomy.—The indications, technique and results were illustrated by a film.

Resection of utero-sacral ligaments.—This, one of the original sympathetic operations, has recently been revived with apparently good results. It is simple and effective in selected cases of pelvic neuralgia, but carries the risk of damage to the detrusor nerves of the bladder.

Ovarian sympathectomy.—This procedure advocated for the relief of pain of ovarian origin (ovulalgia), "Mittelschmerz", "ovarian dysmenorrhœa", &c., consists essentially in division of the nerve supply to the ovary; originally a tedious dissection of the nerve fibres in the infundibulo-pelvic ligament, it has recently been simplified to simple excision of 1 cm. of the whole ligament itself. Though widely advocated, the author's experience is that it is of little, if any, clinical value, and probably does actual harm by severing some of the control necessary for complete ovulation.

Intrathecal alcohol injection.—This is an occasionally valuable procedure for the relief of intractable visceral pain in recurrent carcinoma. It carries with it, however, the considerable risk of producing lower limb and bladder paralysis.

Mr. G. W. Theobald:

Pain may be regarded as an entity (and study along these lines is rewarding), as a guide to diagnosis, or as the most common symptom which clamours for relief. Pelvic pain is frequently associated with menstruation, but much of it is related to exercise and indirectly to the time of day, or may occur in association with micturition, defæcation, or coitus. On the other hand, iliac fossa pain may occur at very irregular and unpredictable intervals. It is important to bear in mind that constipation, colitis, and pathological changes in the renal tract may provoke unexplained pelvic pain.

In dysmenorrhœa the first period is rarely painful, and the pain may not start until months or years later. The onset of the pain may occur from half an hour to fourteen days before, and disappear with the flow, or it may commence with the flow and last either for a few hours, or until the period finishes. It may not commence until the second day or until the end of the period, and there are a few people who are never free from pain except when menstruating. In Bradford, dysmenorrhœa is hardly encountered in the mills and factories and is predominantly an affliction of typists.

Strain, study and hectic living may cause a woman to have a series of very painful periods although she normally suffers no discomfort. A famous swimmer stated that if she had to swim a race at the beginning of her period the flow stopped immediately and her next period was always painful. Conversely, women who invariably suffer from severe dysmenorrhœa nearly always have painless periods when they are brought into hospital for investigation.

Dysmenorrhœa has been cured by falling in love, by childbirth, by various operative procedures and by hormones, those used being progesterone, œstrogen and U.R.F. It is important to stress that œstrogen given during the last ten days of the cycle frequently suffices to prevent dysmenorrhœa. This disposes of the unfounded assumption that the onset of

primary dysmenorrhœa, in a girl whose periods were originally painless, is related to the commencement of ovular menstruation.

It may therefore be concluded that there is no direct correlation between dysmenorrhœa and either pelvic congestion or ovulation. Seeing that both primary and secondary dysmenorrhœa respond to similar therapy, I am not disposed to accentuate any difference in ætiology.

Dysmenorrhœa only accounts for a fraction of the pain which arises in the pelvis. The distribution of this pain is usually limited to the lower abdomen, and the inner and outer aspects of the upper portions of the thighs, and posteriorly to the lower sacral area. It may, however, simulate renal pain and even that associated with a gastric ulcer. Pain occurring along the outer border of the rectus abdominis muscle on either side, and at points where muscles are attached to the bony pelvis, or Poupart's ligament, may result from trauma and be strictly analogous to a tennis elbow. Similar traumatic pain may occur at many points on the back.

The most common type of pain is described as "nagging" like a toothache, while that associated with dysmenorrhœa may be "cramp-like". Patients occasionally describe the occurrence of sharp, breathtaking pain, which causes them to hold on to any available support. This sharp pain soon passes off, often completely, but may persist for several hours as a dull, nagging pain.

In the abdominal examination the distinction between pain and tenderness is important. Pain in the lower abdomen, and lower sacral region, unassociated with any area of tenderness, is clearly referred from some viscus. Tenderness which disappears when the abdominal musculature is tensed, is also referred, but the pain which persists in spite of taut musculature may arise wholly in the abdominal wall, or may contain a component of referred visceral pain.

On vaginal examination, movement of the cervix should cause neither pain nor discomfort. On the other hand it may provoke severe pain. The cervix can be moved in six different directions, and the different movements may provoke pain in four or five different sites. Such observations may often be made in a patient whose cervix appears to be healthy and in whose pelvis no abnormality can be detected. It may be observed, in parenthesis, that one of the main distinctions between primary and secondary dysmenorrhœa is that movement of the cervix in the former type is invariably painless, whereas in the latter it always provokes pain. It is apparent that the pain provoked by moving the cervix must arise in the parametric tissue, for it would otherwise be impossible to account for the fact that different movements provoke pain in different sites. Pain so provoked is frequently, but by no means invariably, the pain of which the patient complains. This is particularly true of dyspareunia caused by deep penile penetration.

On bimanual examination, the ovary is often found to be exquisitely tender. From time to time, however, it proves possible to move it into a position where quite strong pressure on it causes no discomfort. Further, when the abdomen is opened under local anæsthesia, it can be demonstrated that palpation, squeezing with an ovum forceps, and even the injection of enough saline solution to distend its capsule, cause no pain. It is suggested that so-called ovarian pain arises in the extension of the parametric tissue which spreads in between the leaves of the broad ligament.

Pain arising in the pelvic organs, including the bowel, and the parametric tissue, can be abolished, even if only for the time being, in three distinct and separate ways:

(1) By infiltrating the ilio-hypogastric and ilio-inguinal nerves with a local anæsthetic.

(2) By infiltrating the parametric tissue with lignocaine. Pain caused by the injection is of course transitory, but it may "shoot" into the renal angle, into the hypochondrium and down to the knee, and this phenomenon is most striking.

(3) By cauterizing the internal os uteri with the silver stick.

The first procedure anæsthetizes mainly somatic nerves, the second autonomic nerves, while the third overstimulates autonomic nerves.

Further, uterine pain, indistinguishable from dysmenorrhœa, can be provoked by delivering a faradic current to the endocervix or endometrium, of so weak an intensity that it cannot be appreciated on the skin of the forearm or face. This pain can be relieved by raising an anæsthetic wheal, with either procaine or lignocaine, on the skin of the abdomen, in the midline, about 1½ in. (3·8 cm.) above the symphysis pubis. As the intensity of the current is increased a wider area of cutaneous anæsthesia is needed to abolish the pain. A point is soon reached when the pain cannot be abolished, but it is nevertheless referred to the same cutaneous area although it is completely anæsthetic. It is likewise easy to abolish the pain of dysmenorrhœa by raising an anæsthetic wheal on the same cutaneous area of the lower abdomen.

Before presenting conclusions it is worth referring to certain phenomena which may be associated with cauterization of the internal os uteri with the silver stick. In the first place autonomic nerves, other than those which mediate pain, may be stimulated. The woman

may not experience any pain as the result of this procedure, at any rate in the first instance. She may, however, vomit, and become covered with a cold sweat, while her pulse-rate may fall to about 40 a minute and her blood pressure to about 80/50 mm.Hg. This denotes a well-recognized physiological state in which the muscle capillaries are dilated and the venous return to the heart is severely diminished.

Apart from these rather frightening phenomena, which never occur if the patient is satisfactorily under the influence of self-induced trilene analgesia, it may be observed that cauterization of the cervix is remarkably efficacious in relieving frequency and urgency of micturition and stress incontinence of urine, provided no gross mechanical factors are operating.

In a healthy woman who complains of no pain at all, cauterization of the cervix provokes pain in the mid-line which spreads over the lower abdomen. If a woman complains of pain in one or other iliac fossa, this treatment frequently exacerbates her pre-existing pain, and is experienced nowhere else. If the sole reason for the cauterization is lower sacral backache, it may provoke an increase in the backache, but usually causes lower abdominal pain. If, however, the ilio-hypogastric and ilio-inguinal nerves are then infiltrated with a local anæsthetic, the abdominal pain is abolished and the backache becomes unmasked. This phenomenon of unmasking of pain can be most frequently demonstrated during labour.

It may also be observed that cauterization of a sinus in the vault of the vagina, subsequent to total abdominal or vaginal hysterectomy, may not only cause the same pain as cauterization of the cervix, but may cure long-standing and intractable abdominal pain. One such patient was so cured of severe pain in the right iliac fossa, of twelve years' duration, for which she had suffered four operations; appendicectomy, ventral suspension, oophorectomy, and finally, total hysterectomy. One patient complained, not only of dyspareunia, but of severe vomiting immediately after intercourse. A Mersilene ligature, left after vaginal hysterectomy, was removed, and she had no further trouble.

The practical claim which emerges from this very brief report is that iliac fossa pain, lower abdominal pain, dysmenorrhœa (both primary and secondary), dysuria, painful defæcation, and even pain in the hypochondrium and renal angle, together with frequency and urgency of micturition and stress incontinence of urine, may, in a high percentage of cases, be cured by cauterization of the internal os uteri with the silver stick, combined with the intelligent use of a local anæsthetic.

Injection of a local anæsthetic into the sacro-iliac ligaments may not only relieve backache, but also iliac fossa pain on the same, or even on the opposite side. Relief of pain may, moreover, serve to regularize the periods. The approach to the problem is constantly changing and more recently lignocaine has been used for infiltrating the ilio-hypogastric and ilio-inguinal nerves, and for injection into the parametric tissue. It is possible that these simple procedures may often be applicable in lieu of cauterization of the cervix, and they would clearly be of inestimable value in the presence of chronic inflammatory conditions (should cauterization of the cervix be contra-indicated) and after hysterectomy. Some of the results obtained have been quite dramatic, and dysmenorrhœa and urge incontinence of urine have been "cured", for at any rate some time, by the former procedure. It is, however, at present too early to assess the permanent value of these techniques. A number of cases of dysmenorrhœa have, however, been permanently cured by injecting an appendix scar, or a tender area in the abdominal wall, with a local anæsthetic. It must further be remembered that even an ordinary curettage in a multigravida may suffice to cure pain and even stress incontinence of urine.

Infiltration of the ilio-hypogastric and ilio-inguinal nerves with lignocaine is, moreover, useful in relieving acute lower abdominal pain associated with tubo-ovarian inflammation and other acute conditions. The same local anæsthetic, suitably injected, abolishes the pain of a Bartholin's abscess.

Further, the injection of a local anæsthetic can be used to differentiate between pain arising in the pelvis and appendicitis, while injection of lignocaine into the parametric tissue makes it possible to distinguish clearly between a small tubo-ovarian mass and spasm in the adnexa.

The pain signals are so elaborated in the cerebral cortex that they bear little resemblance to the final image or pattern. The pain image or capacity is compounded of imagination, fear, and such environmental factors as the lurid press, the cinema, aspirin and even the health service. We know, too, that advanced malignant growth, extensive endometriosis or massive adhesions may be present in the pelvis without causing pain, and conversely that severe and crippling pain may be associated with apparently normal pelvic organs.

It is suggested that pelvic pain may arise because of insults, either to the cerebral cortex, or to the pelvic organs and may be cured either by central suggestion (including hypnosis), or by overstimulating or anæsthetizing pelvic sympathetic nerves. It follows that surgical intervention, which is not always successful, should be used only as a final resort in the treatment of pain unassociated with detectable changes in the pelvic organs.

Section of Epidemiology and Preventive Medicine

President—IAN TAYLOR, M.D., M.R.C.P., D.P.H.

[*November* 16, 1956]

DISCUSSION ON THE EPIDEMIOLOGY OF CANCER

Dr. J. Knowelden:

Cancer in Kampala

It has been widely held that the pattern of cancer in Africans was different from that in white races, in particular in the high incidence of primary liver cancer, but it was also thought that in general malignant disease was rare in Africans. Dr. J. N. P. Davies, Professor of Pathology, and his colleagues at the Makerere College Medical School in Uganda, with the support of the British Empire Cancer Campaign, set up the Kampala Cancer Registry with the object of providing reliable evidence from the surrounding Mengo District to check these beliefs. I was invited to Uganda for a period of two months early in 1955 to see the registry and to advise on its future development.

The Registry was set up initially as a retrospective study of the Kampala hospital records in 1952 and 1953, but since 1954 it was reorganized as a current registry of in-patients. These hospitals—Government African, Asian and European and two large Mission hospitals—make Kampala the main hospital centre as well as commercial focus for the country. The quality of the medical information obtained is high, is backed by the Government and Medical School pathological departments and, as it is provided by a few clinicians only, is probably more uniform than would be found in a larger registry. The main problems lie rather in recording the identification particulars of the patients. The sick African, like his counterpart here, is liable to go the rounds of hospitals if he thinks he has not got satisfaction, but he confuses the trail by being unconcerned how he spells his name. A careful check has to be made to prevent duplicate entries of the same case from the different hospitals. It is common experience, too, that many Africans have little idea of their age, and even educated Africans have great difficulty in estimating accurately the age of their own tribesmen. Consequently rather crude approximations have often to be accepted. Finally, it is often difficult to establish the true place of residence, particularly if the patient is an immigrant from such distant places as the Belgian Congo and still speaks an unfamiliar dialect.

As a guide to the working of the registry we made a provisional analysis using the cases registered in the three years 1952–54 and the data from the 1948 census of Uganda. The data on cancer in the Asian and European populations is so scanty that I will deal entirely with the African picture. Table I shows the average annual age-specific incidence rates in

TABLE I.—INCIDENCE OF CANCER, ALL TYPES, IN MENGO DISTRICT, 1952–54
(Average annual rates per 10,000)

Age (years)	Males		Females	
	Cases	Rate	Cases	Rate
1–5	6	0·39	8	0·51
6–15	20	0·69	10	0·46
16–45	201	2·40	171	2·87
46 and over	193	9·09	101	6·60

TABLE II.—RELATIVE INCIDENCE OF CANCER, ALL TYPES, IN DIFFERENT PARTS OF MENGO DISTRICT, 1952–54

	No. of cases Registered	Expected	Regd./Expd. %
Males			
Kyadondo ..	167	64·2	*260*
Busiro and Kyaggwe	118	148·5	*79*
Other Sazas	135	207·3	*65*
Females			
Kyadondo ..	98	41·6	*236*
Busiro and Kyaggwe	96	97·4	*99*
Other Sazas	96	151·0	*64*

each sex for all types of malignant disease. The age-groups used were determined by those reported in the census, 1–5 years is childhood, 6–15 years the age at which children help in minding cattle or in domestic tasks, 16–45 years adult working life and 46+ old age—I have omitted the infants as hardly any cases were reported in this youngest group. The cheering picture was obtained that at least there was an age-gradient and perhaps our crude age-groups were meaningful.

The country is divided into numerous sazas, or counties, each under a native chief, Mengo District having 12 such sazas. We applied the age-specific incidence rates for the whole of

Mengo District to the census populations of each saza to obtain the expected number of cases which we then compared with the number registered among residents of these areas. We found wide variations in reported incidence as indicated by the ratios of registered to expected cases for each saza. I have summarized the pattern in Table II by showing Kyadondo separately (the saza in which Kampala lies), Busiro and Kyaggwe together the two nearest to Kyadondo with easiest communication with Kampala, and the remaining nine as the third group. In both sexes Kyadondo had about 2½ times the expected incidence, Busiro and Kyaggwe about average for the whole District and the remaining sazas lowest incidence. We considered whether these differences might have been caused by changes in population distribution since 1948 or by over-reporting of Kyadondo addresses by temporary residents, but eventually concluded that these factors could not be responsible. Instead we believe that easy access to Kampala hospitals by Kyadondo residents, and possibly their greater sophistication, gave better reporting than we could expect from a more distant entirely rural population. It is, therefore, proposed that the Register in future concentrates on this saza and takes special steps to check on such details as the stated residence of patients.

In Table III I have attempted a comparison between incidence in Kyadondo in 1952–54

TABLE III.—COMPARISON OF INCIDENCE OF CANCER, ALL TYPES, IN KYADONDO, 1952–54, AND IN DENMARK, 1942–44

(Average annual rates per 10,000)

Kyadondo		Denmark	
Age	Rate	Age	Rate
	MALES		
1–5	0·5	0–4	1·62
6–15	2·7	5–14	0·85
16–45	6·0	15–44	4·43
46+	24·3	45–54	22·57
	FEMALES		
1–5	1·6	0–4	1·08
6–15	0·3	5–14	0·64
16–45	7·0	15–44	8·19
46+	15·3	45–54	35·72

and in Denmark in 1942–44, as reported by the Danish Registry. There is a surprising similarity in male rates for the age-groups (these are not identical but are sufficiently close not to disturb this comparison): and in females the chief difference is in the oldest group. Some under-reporting in old women is to be expected as it appears to be general for them not to report to hospital when sick so readily as men of the same age. I was told also that uterine cancer was rarely seen until a specialist gynæcological unit was started at Mulago, but is now increasingly registered. It may be that these cancers are still under-reported.

As a final picture of the results being obtained I have compared the Kyadondo and Danish incidence in certain broad selected sites. To do this I have applied the Danish age-specific rates for each cause to the Kyadondo population and have shown in Table IV the total thus

TABLE IV.—COMPARISON OF INCIDENCE OF CANCER OF SELECTED SITES IN KYADONDO, 1952–54 WITH THAT EXPECTED AT DANISH RATES, 1942–44

	Males		Females	
Site	Registered cases	Expected cases	Registered cases	Expected cases
Skin	14	10·5	4	5·9
Gastro-intestinal ..	18	35·4	10	20·1
Liver	26	2·0	2	1·9
Kidney, bladder, &c.	19	13·1	2	2·0
Penis	11	1·2	—	—
Breast	—	—	9	30·7
Ovary and tubes ..	—	—	12	10·6
Uterus	—	—	28	43·5
Lymphatic system ..	22	10·2	4	5·4

expected in Kyadondo with the numbers observed. Here the outstanding differences are an excess of liver and penile cancer in men, a deficiency of gastro-intestinal cancer in both sexes, and a deficiency of breast cancer in women.

These results are provisional and too much emphasis must not be placed on them. The Kampala registry is continuing for several years and it is hoped to have recent and reliable census data available by 1958 when several years' data will have been accumulated. I hope I have said enough to indicate the considerable problems involved in the work Dr. J. N. P. Davies and his colleagues have undertaken, and also the excellent promise of valuable information which has been afforded by their initiative.

Dr. Alice Stewart:

A Current Survey of Malignant Disease in Children

The decision to make an environmental survey of leukæmia in childhood (by interviewing parents after the death of the child) was taken after a close scrutiny of official vital statistics (Hewitt, 1955) had shown the nature and extent of the rise in the death-rate at all ages (Fig. 1) and at ages under 5 (Fig. 2). The unusual peak of mortality in the 2nd and 3rd years of life (which has been more marked in recent years) was the main reason for restricting the survey to young children and for focusing attention on antenatal X-ray histories. Children who had died from other cancers were originally included in the survey as a contrast group, but subsequent examination of vital statistics has shown that for young children, these deaths also have an unusual age distribution (Fig. 3).

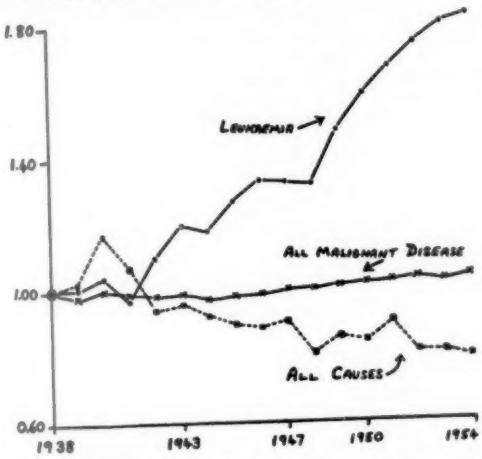


FIG. 1.—Course of the comparative mortality index for certain causes of death, 1938=1·00.

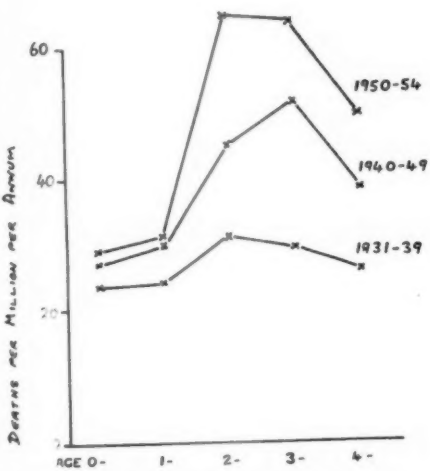


FIG. 2.—Mortality of young children from leukæmia in three different periods.

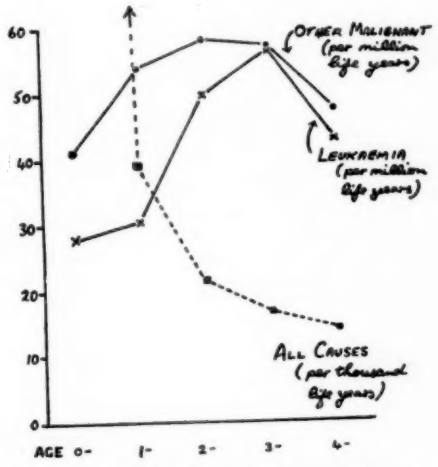


FIG. 3.—Mortality from certain causes at ages under five, England and Wales, 1940–1954.

Even the field work of the survey is not yet completed, but all Local Authority Health Departments in England and Wales are co-operating and an attempt is being made to cover

all cancer and leukæmia deaths under 10 years of age reported in the three years 1953–55. These comprise:

	Cases
Leukæmias	794
Neoplasms of brain and spinal cord ..	269
„ „ kidneys	155
„ „ suprarenals	136
„ „ lymph nodes	133
„ „ other sites	193
Total	1,680

For each of the cases included in the survey there will be a live control matched for age and sex, but otherwise picked at random from a local list of births. Thus far, most of the control children have been first choices, but removals, infant deaths, &c., have occasionally necessitated taking several names from a birth list. Unless they have moved out of the Local Authority area since the child's death, the parents of each case-control pair are being interviewed by one and the same doctor. The questionnaires for the children who have died are designed to elicit information about the child's health before the onset of the fatal illness, and the mother's health before and during the relevant pregnancy. All investigations and treatments are recorded, and wherever possible X-ray data are checked with hospital notes. A note is also made of any cases of leukæmia and malignant disease in the family, any degree of consanguinity between parents and grandparents, and certain features of the child's diet and home background. The schedules for the controls ensure that the same facts are obtained up to the age when the corresponding case first showed signs of the fatal illness.

By November 1, 1956, only 1,072 case-control pairs had been interviewed. The records of these interviews still await detailed analysis, but preliminary inspection has revealed two points of considerable interest. In the first place a history of irradiation *in utero* (i.e. an ante-natal *abdominal* X-ray) was obtained nearly twice as frequently from the mothers of children who had died from leukæmia or cancer as from the mothers of live controls (*see* Table I). Secondly there were, among the 515 cases of leukæmia, 15 children who were mongolian idiots.

TABLE I.—MALIGNANT DISEASE IN CHILDHOOD AND DIAGNOSTIC IRRADIATION *In Utero*

Group	Number of children	Children irradiated *in utero*	
		Number	Per cent
Controls	1,072	79	7·4
Cases of:			
Leukæmia ..	515	63	12·2
C.N.S.	168	20	11·9
Renal	103	16	15·5
Neuroblastomas	91	18	19·8
Lymph nodes ..	70	6	8·6
All other sites	125	20	16·0
All cases of malignant disease	1,072	143	13·3

The reasons for the excess of "irradiated fœtuses" among the cases will remain uncertain until a more detailed examination of the records has been made. But it is already clear that the difference between the cases and controls in this respect is not due to differences in birth, rank or social class nor to differences in maternal age. The most likely explanation is that total body exposure to small doses of ionizing radiations shortly before birth causes a significant increase in the risk of developing leukæmia or cancer in childhood (Stewart, Webb, Giles and Hewitt, 1956). No explanation of the excessive liability of mongols to leukæmia can be offered at this stage, but the association between the two diseases appears to be independent of any history of irradiation and has already been noted by other workers (Krivit and Good, 1956; Merrit and Harris, 1956).

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Dr. R. A. M. Case, *Chester Beatty Cancer Research Institute, London,* read a paper on:
"The Present Relevance of Cramer's Hypothesis."

Section of Comparative Medicine

President—DOUGLAS MCCLEAN, M.B., M.R.C.S.

[*December* 19, 1956]

DISCUSSION ON TUBERCULIN SENSITIVITY

Dr. A. B. Paterson (Weybridge):

The Tuberculin Test in Tuberculosis-free Cattle

It has long been known that reactions to tuberculin can occur in cattle free from tuberculosis and the existence of these so-called non-specific reactions was indicated by Bang and by Hastings at the beginning of the century. The use of high doses of tuberculin of increased potency in the intradermal test, and decrease in the incidence of tuberculosis both helped to increase difficulties of interpretation, and, in addition, about 1925 there came a wider appreciation that mycobacteria other than those of bovine type might sensitize to mammalian tuberculin (Bang, 1936; Hastings, 1912–13; Plum, 1925). Since then much work has been devoted both to causes of heterologous sensitizations and to aids in the interpretation of reactions to mammalian tuberculin.

One of the most valuable aids has been the use of avian tuberculin, and since 1940 it has been used in the United Kingdom simultaneously with mammalian tuberculin in all official tests connected with the attested herds scheme (Ministry of Agriculture, 1942). The "comparative" test permits interpretation of reactions to mammalian tuberculin in herds believed to be free from tuberculosis—such reactions, if accompanied by strong reactions to avian tuberculin, must be interpreted with caution after taking fully into account the history of the herd and its environment.

I shall give briefly the known causes of non-specific tuberculin sensitization in cattle, and, in view of the current interest in human medicine in geographical distribution of tuberculin sensitivity, I shall present a picture of its incidence and occurrence in cattle in two areas of England.

Causes of Non-specific Sensitization in Cattle

(1) *Avian type tubercle bacilli* may produce tuberculin sensitivity without lesions, the sensitivity disappearing with removal of the infecting source. Occasionally lesions or even generalized tuberculosis may occur.

Sources of avian tubercle bacilli are:

(*a*) Tuberculous poultry; (*b*) swine (of little importance); (*c*) birds other than poultry—pigeons, gulls, sparrows, starlings, wood-pigeons, pheasants and crows (pigeons, wood-pigeons and sparrows may harbour avian type tubercle bacilli apparently without having contact with infected poultry); (*d*) rats.

The avian type tubercle bacillus can be transmitted by such agencies as fly larvæ (Feldman, 1938).

(2) *M. johnei.*—Well known as the cause of a chronic enteritis in cattle (Johne's disease) and allergically related to the avian type of tubercle bacillus. Experimental and natural cases of Johne's disease show early sensitivity to avian tuberculin which disappears with progress of the disease.

(3) *So-called "skin tuberculosis".*—This is a benign disease of cattle in which lesions commonly occur on the skin of the legs as nodular granulomata, which may contain a yellowish pus. The lesions contain uncultivable mycobacteria (Robertson and Hole, 1937; Hole and Hulse, 1939). Sensitivity, to mammalian rather than avian tuberculin, has been produced experimentally in cattle inoculated with lesion material.

(4) *Human tubercle bacilli*, derived from infected human subjects, produce sensitivity to mammalian tuberculin which disappears with removal of the source of infection and is less marked on re-test (Stenius, 1938).

BCG and the vole bacillus produce sensitivity to mammalian tuberculin.

(5) *Saprophytic mycobacteria.*—It is debatable whether such saprophytic species as *Mycobacterium phlei*, *M. smegmatis*, &c., can render cattle sensitive to tuberculin. Experimentally they sensitize cattle only when injected along with an oily adjuvant. Whether intermediate types such as *M. ulcerans* or *M. balnei* are of importance is not known.

(6) *Organisms other than mycobacteria.*—*Actinobacillus lignieresi* and *Br. abortus* have been reported as causal agents of sensitivity to tuberculin in cattle in the field, but sensitivity could not be produced experimentally with *Corynebacterium pyogenes*, *Actinomyces bovis*, *Actinobacillus lignieresi* (Buxton and Glover, 1939). Non-specific sensitivity is apparently not produced in infections with the liver fluke, *Fasciola hepatica*; during migration of larvae of the warble fly, *Hypoderma bovis*; or by hydatid cysts. It does not result from vaccination with avirulent *Brucella abortus* (Strain 19 vaccine), or from histoplasma infection.

(7) *Physiological causes and natural hypersensitivity.*—Cattle apparently do not readily develop tuberculin type sensitivity of high order.

(8) *Reactions caused by tuberculin itself.*—Phosphate-diluting fluids apparently potentiate a reaction, but produce very small reactions when injected alone.

Despite the many investigations of non-specific reactivity to mammalian tuberculin, it is difficult to obtain a clear picture of the degree to which it occurs, and my colleague, Miss Hebert, and I therefore attempted some quantitative arrangements of data obtained from the records of routine tuberculin tests in herds tested under the "Attested Herds Scheme". Samples of 100 herds in Berkshire and of 200 herds in Cumberland were taken. All herds in both samples had been accepted as free from tuberculosis (Hebert and Paterson, 1955; Paterson and Hebert, 1957). Since the comparative test is always used, a contrast can be drawn between the reactivity to avian and mammalian tuberculins in the two counties. The test itself comprises the intradermal injection of avian and mammalian PPD tuberculins at respective strengths of 0·5 and 2·0 mg./ml., each in a dose of 0·1 ml. Injections are made in the skin of the middle third of the neck, and measurements are made of the thickness of the double fold of skin at the injection sites before and 72 hours after injection. The difference, in millimetres, between the first and second measurements constitutes the degree of reaction.

The data were analysed and histograms and graphs prepared to illustrate (*a*) the percentage of animals giving different degrees of response to avian and mammalian tuberculin in the two areas, (*b*) variation in reactions in age groups, (*c*) influence of proximity of herds to woods and trees, (*d*) effect of altitude, (*e*) effect of geographical regions, (*f*) influence of "skin tuberculosis", (*g*) influence of sex, and (*h*) of some other factors.

[These histograms and graphs were shown on slides and are not reproduced here. The conclusions arrived at as a result of this study were discussed by Dr. Paterson.]

Frequency Distribution of Reactions

This study indicated that the degree of non-specific reaction to mammalian tuberculin in the two counties was the same but the reaction to avian tuberculin differed significantly. If the non-specific response to mammalian tuberculin parallels the avian reaction then the avian agency must be more efficient in Cumberland than in Berkshire.

Reactions of Age Groups

When the mean reactions of animals in the samples were arranged according to age, some striking similarities and differences were revealed.

(1) In both areas the response to mammalian tuberculin was always broadly parallel with that to avian tuberculin.

(2) In Cumberland avian reactivity rose rapidly to a peak at 4 years of age with a slight downward trend to 10 years of age. In contrast, in Berkshire a much higher peak was reached by 3 years, the higher reactivity being significantly different at ages of 1, 2, 3 and 4 years.

(3) In Cumberland, the curve of reactivity to mammalian tuberculin slowly rose to a peak at 8 years of age. In Berkshire cattle, the curve of reactivity started below the Cumberland curve, rose above it to a maximum at 3 years, crossed below between 5 and 6 years of age and reached a minimum at 9 years.

The curves for non-specific reactions to mammalian tuberculin suggest that either quality of the sensitizing agent or the mechanism producing sensitivity differs in the two areas.

Proximity to Trees and Woods

Smith (1955) has suggested that the incidence of non-specific reaction is higher in cattle in wooded regions than elsewhere and has related this to the presence of wood pigeons which are known to harbour mycobacteria closely related to the avian tubercle bacillus. The graphs for Berkshire support this suggestion but in Cumberland this is not so and factors other than woodlands appear to be of greater influence.

Effect of Altitude

Increasing altitude appears to decrease the incidence of non-specific reactions. The effect being more marked in Cumberland with altitudes of 1,000 ft. and over, than in Berkshire where altitudes rise to only 600 ft.

Effect of Geographical Regions within the Two Counties

In Berkshire, except for a rather higher reactivity to avian tuberculin in the Windsor region, there was little difference from area to area. In Cumberland there was a definite drop from the low-lying coastal land in the west to the higher areas in the east. Here altitude and regional effects go together. The altitude effect, for some unknown reason, is most marked in calves.

Skin Tuberculosis

The incidence was about 1% in both counties. Tuberculin sensitivity appeared at an early age and was more marked to mammalian tuberculin at all ages. The highest sensitivity appeared at an earlier stage than the maximum incidence of the disease.

Effect of Sex

Male animals in Cumberland had a higher degree of reactivity to avian tuberculin than those in Berkshire, probably because in Cumberland bulls are kept at pasture, whereas in Berkshire they are usually housed.

Other Factors Examined

Neither the keeping of pigs or poultry on the farm, nor the breed of cattle appeared to have any marked influence on the incidence of non-specific reactivity.

Conclusions

The picture of non-specific reactivity to mammalian tuberculin in this study confirms that such reactions are usually linked to reactivity to avian tuberculin which is almost certainly caused by *Mycobacterium tuberculosis* var. *avian* or the related *Mycobacterium johnei*. The difference in the data from the two counties as revealed by the graphs may be an indication of the relative incidence of these two agents in these counties. The major factor determining the development of non-specific reactions appears to be contact with a warm-blooded host infected with and excreting mycobacterium. Little is known of the influence of route of infection or of the quantity and frequency of the infecting dose on the products of non-specific reactivity. There is little evidence that saprophytic or intermediate types of mycobacteria are concerned; experimentally they can cause tuberculin sensitivity only when given in massive doses or in conjunction with an adjuvant substance. Organisms other than mycobacteria have been suspected only when a distinctive granulomatous type of lesion is produced (Paterson, 1956).

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Dr. T. Francis Jarman (Medical Director, Mass Radiography Service, Welsh Regional Hospital Board):

Tuberculin Testing in the Control of Tuberculosis

When Robert Koch discovered tuberculin in 1890 great hope was placed in its possible usefulness as a therapeutic agent, a hope which proved to be unjustified. Von Pirquet in 1906 first described its use to detect persons infected with the tubercle bacillus.

The use of tuberculin for this purpose has been of the very greatest importance in the control of tuberculosis. There are, at present, two ways in which it is used—diagnostically in individuals and as an epidemiological technique in the study and control of tuberculosis in the community. Certain aspects of tuberculin testing have recently come much to the fore and it is with these that I propose to deal in some detail.

The Reliability of the Test

Myers (1946) declares that "as an epidemiological agent the test excels every other procedure" relative to tuberculosis. Meyer and others (1951) have shown that error in the

reading of the tests is very small. In the first survey in the Rhondda Fach, 1,228 tests were read by two observers for qualitative results and in only one case was there any discrepancy in the readings (Jarman, 1953).

Palmer and his associates (1950) first drew attention to the possibility of non-specific reactions to human tuberculin. In recent years 43 million tests have been carried out under the direction of the World Health Organization and its Tuberculosis Research Office. Their teams have paid particular attention of late to the problem of non-specific, or false positive, reactions. It appeared to them that methods similar to those employed by the veterinarians for the purpose of separating cattle with specific and non-specific tuberculin sensitivity might be used in the study of non-specific sensitivity in man (WHO Tuberculosis Research Office, 1955). Discrepancies in the frequencies of weak-dose and strong-dose reactors to human tuberculin in different geographical areas suggested that persons with strong-dose reactions could be regarded as having non-specific sensitivity. A special TRO team tested more than 3,000 persons with serial doses of both human and avian PPD tuberculin corresponding to 1, 10, and 100 T.U. Results from these comparative tests indicated that the tuberculin sensitivity in the populations studied must be caused by different sensitizing agents. The low-degree sensitivity was brought out more effectively by avian tuberculin and the high-grade sensitivity by human tuberculin. However, those with high-grade sensitivity (i.e. those reacting to a small dose) can undoubtedly be regarded as having specific sensitivity caused by infection with virulent tubercle bacilli. Positive reactions to either 5 or 10 T.U. can, therefore, be regarded, for practical purposes, as specific positive reactions (WHO Tuberculosis Research Office, 1955).

The need to develop a simple test which can be given by relatively untrained persons has led to the development of the multiple puncture test using undiluted Old Tuberculin (Heaf, 1951). Comparisons have been made between this test and the intradermal Mantoux method (Jarman, 1953). This work and recent studies by Gillis and Stradling (1957) on double observer reading of the tests illustrate the difficulty of establishing the lowest category of reaction to this test which can be considered as positive and which is reproducible. Nevertheless, the Heaf test has proved easy to administer and extremely valuable in practice and its use is increasing. Studies to compare the prevalence of positive reactors to the Heaf test in mass tuberculin testing with that obtained by using 5 T.U. by the intradermal technique might give useful information as to the possibility of non-specific reactions produced by the former.

Mass Tuberculin Testing as a Reflection of Tuberculous Infectivity in a Community

The percentage of positive reactors in different age groups presumably reflects the degree of tuberculous infectivity in a community and good evidence exists to support this. Recently, in the town of Monmouth the number of new cases of pulmonary tuberculosis notified rose sharply in excess of what was expected especially in the age group 15–20. A mass radio-

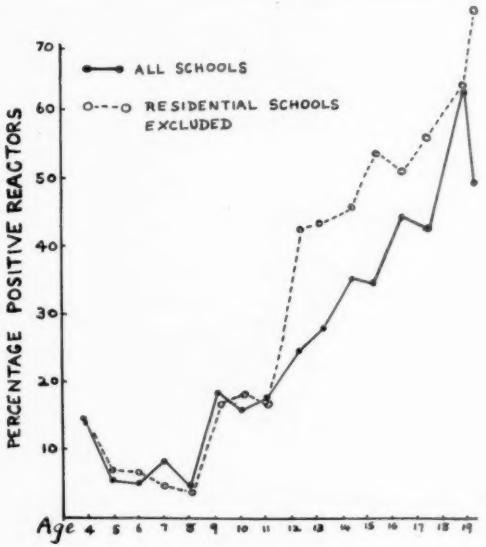


FIG. 1.—Results of tuberculin testin in Monmouth.

graphy survey of the total community type (Cochrane *et al.*, 1952) was therefore carried out and 89% of the population were X-rayed. The prevalence of active tuberculosis was highest in the age group 15–24, viz. 15 per 1,000 and this was to some extent reflected in the results of the overall tuberculin testing but became more evident when the residential schools were excluded (Abraham *et al.*, 1955) (Fig. 1). Tuberculin testing in the Calder Valley (Keidan *et al.*, 1952) when compared with that done in Leeds and in the Rhondda Fach shows how the excessive amount of non-respiratory infection in the Calder Valley was reflected in the prevalence of positive reactors (Fig. 2). Griffith (1956) showed that 35% of children aged

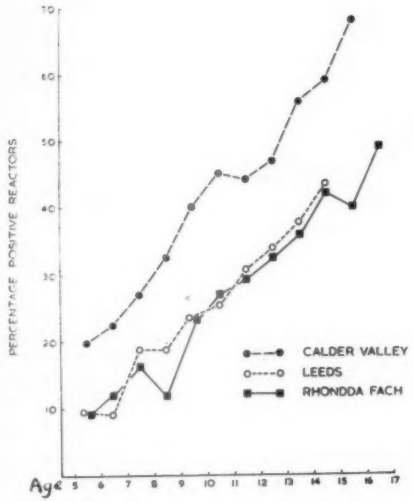


FIG. 2.—Results of tuberculin testing in the Rhondda Fach compared with those of the Calder Valley and Leeds.

5–13 from two schools in the docks area of Cardiff reacted positively to tuberculin testing whereas only 24% of children aged 12–13 from all other Cardiff schools were positive. The difference between these rates is reflected in the findings of mass radiography surveys in these districts (Welsh Regional Hospital Board, 1956). In the population of the docks area 8 new cases of pulmonary tuberculosis were discovered for every 1,000 persons examined in contrast to Cardiff where only 2 new cases were discovered for every 1,000 examined. Tuberculin testing can, then, be useful to ascertain the likely size of an existing tuberculosis problem, especially in relatively backward areas where mortality and prevalence are high. Benjamin (1955) has emphasized the importance of such survey techniques in India. In the mass tuberculin testing done during the International Tuberculosis Campaign the prevalence of positive reactors was used primarily for selecting persons for vaccination but the results also reflected the probable tuberculosis situations in the various countries. The frequency of positive reactors in the age group 7–14 years varied from 13% in Costa Rica to 75% in Hong Kong. The percentages were lowest in the American countries, highest in the Far East, and intermediate in the Near East and Africa.

The results of repeated tuberculin testing in a community can be extremely useful as a measure of progress in tuberculosis control and it is for this, amongst other reasons, that Myers *et al.* (1955) and Gedde-Dahl (1956) are opposed to the use of BCG in low prevalence areas such as Minnesota and certain regions in Norway. Myers and others (1955) have shown that tuberculin testing of grade school children once in ten years since 1926 has served as an accurate measure of the effectiveness of the tuberculosis control programme in Minneapolis. In 1929, 47·3% of the children reacted to tuberculin; in 1936, 18·9%; in 1944, 7·7%; and in 1954, 3·9%. The results of tuberculin testing in the two Rhondda Fach surveys also illustrate this (Jarman, 1955). At the time of the second survey the overall prevalence of infectious pulmonary tuberculosis had been reduced to a greater extent than in a "control" valley and this is shown in Figs. 3 and 4 and Table I. The results of follow-up testing in school children are shown in Tables II, III, IV and V. The most interesting feature in these tables is the high rate of reversion amongst the school children in the Rhondda Fach as compared with the control valley. It would be interesting to know if such reversion has been observed in cattle.

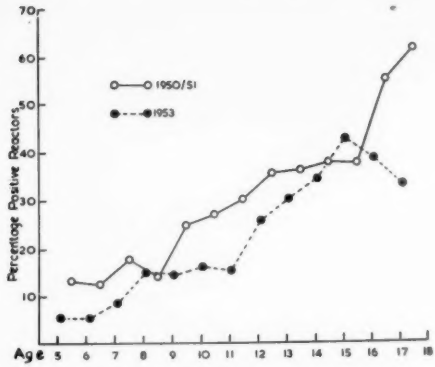


FIG. 3.—Results of tuberculin testing in the Rhondda Fach in 1950/51 and 1953.

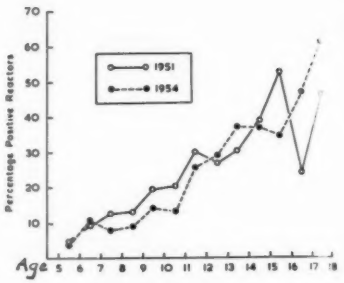


FIG. 4.—Results of tuberculin testing in the control valley.

TABLE I.—STANDARDIZED PERCENTAGE OF POSITIVE TUBERCULIN REACTORS IN THE FOUR SURVEYS, BASED ON THE RESULTS FOR CHILDREN AGED 5 TO 14 INCLUSIVE

Survey	1st in Rhondda Fach	2nd in Rhondda Fach	1st in control valley	2nd in control valley
Standardized percentage positive	24·6	18·4	20·2	18·2

TABLE II.—TUBERCULIN-TESTING OF SCHOOL CHILDREN—RHONDDA FACH. FOLLOW-UP OF THOSE MANTOUX-NEGATIVE IN 1950–1

Age in 1951	No. negative 1950–1	No. tested in both surveys	No. converted negative to positive	% conversion
4–	908	697	37	5·3
8–	865	571	42	7·4
12–15	523	124	8	6·4
Totals	2,296	1,392 (61%)	87	6·3

TABLE III.—TUBERCULIN-TESTING OF SCHOOL CHILDREN—RHONDDA FACH. FOLLOW-UP OF THOSE MANTOUX-POSITIVE IN 1950–1

Age in 1951	No. positive 1950–1	No. tested in both surveys	No. reverted positive to negative	% reversion
4–	131	94	18	19·1
8–	269	181	27	14·9
12–15	303	82	3	3·7
Totals	703	357 (50%)	48	13·4

TABLE IV.—SKIN-TESTING RESULTS IN SCHOOL CHILDREN—CONTROL VALLEY FOLLOW-UP OF THOSE NEGATIVE AT TIME OF FIRST SURVEY

Age in 1951	No. negative first survey	No. tested in both surveys	No. converted negative to positive	% conversion
4–	285	162	6	3·7
8–	561	291	28	9·6
12–15	308	93	6	6·5
Totals	1,154	546 (47·3%)	40	7·3

TABLE V.—SKIN-TESTING RESULTS IN SCHOOL CHILDREN—CONTROL VALLEY, 1954. FOLLOW-UP OF THOSE POSITIVE AT TIMES OF FIRST SURVEY

Age in 1951	No. positive first survey	No. tested in both surveys	No. reverted positive to negative	% reversion
4–	31	20	1	5·0
8–	159	88	2	2·3
12–15	220	69	1	1·4
Totals	410	177 (43·1%)	4	2·2

Tuberculin Testing as a Means of Detecting Source Cases

MacDougall and others (1953) tuberculin tested 3,798 school children between the ages of 3 and 9 years and discovered one previously unknown case of active pulmonary tuberculosis for every 237 tests performed. During 1955–56 in the town of Barry, Glamorgan, 60% of the population were X-rayed by the Welsh Mass Radiography Service. This survey was combined with tuberculin testing of the infant school population, and house contacts of positive reactors were persuaded to attend the unit for X-ray examination (Thomas, 1956). One new case of active pulmonary tuberculosis was discovered amongst the 49 tuberculin-positive children and one from the 290 adult contacts who were X-rayed. This amounts to one new case of active pulmonary tuberculosis discovered amongst adult contacts for every 1,404 tests carried out. The discovery, by radiography, of this one case amongst 397 adult contacts amounts to 2·5 cases per 1,000 examined, which is no more than the rate at which active cases are discovered by routine mass radiography. It would appear, therefore, that this was not a very profitable method of discovering new "source" cases in this town. Ritchie and others (1955), however, used this method in Belfast and found that the prevalence of active tuberculosis amongst adult contacts of tuberculin-positive children was three times as high as that amongst contacts of children who were tuberculin-negative. The usefulness of this case-finding method may be related to the overall prevalence of pulmonary tuberculosis in the community.

Tuberculin testing has been used as a method of discovering source cases by Gedde-Dahl (1952) in work which has become classical. He adopted the method of continuous testing of a whole community in the district of Kim, 100 miles north of Bergen between the years 1937 and 1944. Wherever and whenever a negative reactor was found to have converted to positive a "tuberculosis situation" was deemed to exist and was intensively investigated until the source was discovered. From 272 persons who converted during the period of observation 73 (26%) "intradomiciliary", 130 (48%) "extradomiciliary" source cases were discovered and 70 (26%) could not be traced. This "tuberculin matriculation" technique is, however, applicable to small isolated rural communities rather than densely crowded urban industrial populations.

Use of the Tuberculin Test in BCG Work

In mass BCG vaccination programmes in 26 countries between 1951–1953 in the International Tuberculosis Campaign 43 million persons were tuberculin tested and 16 million vaccinated (WHO Tuberculosis Research Office, 1955). In all cases a single intradermal tuberculin test with 5 T.U. of PPD prepared at the Statens Seruminstitut, Copenhagen, was used as the initial test to separate the infected from those not infected and requiring BCG. The test was read at three to four days and a reaction of less than 5 mm. of induration was considered "negative". BCG-induced tuberculin sensitivity is a problem of considerable theoretical and practical significance. A research programme has been designed by the U.S. Public Health Service (1955) to find out whether the potency of the vaccine, size of the vaccinal lesion, and size of the post-vaccination intradermal tuberculin reaction are related to induced immunity. Studies so far tend to show that immunity is not related to the size of the vaccinal lesion, as a large reaction can be produced by relatively impotent heat-killed BCG, but that it is related to the size of the post-vaccination tuberculin reaction (Tuberculosis Programme, Public Health Service, U.S.A., 1955). A potent vaccine has been shown to produce allergy about as strong as that produced by natural infection which does not appear to wane after intradermal vaccination (WHO Tuberculosis Research Office, 1955). These findings are obviously of the greatest importance, especially in areas of high prevalence.

Use of the Tuberculin Test as a Method of Case Finding amongst Those Actually Tested and Found Positive

Expected immediate morbidity is greater in tuberculin-positive than in tuberculin-negative groups (Palmer and Shaw, 1953). This is especially true of recent converters. In the

Rhondda Fach survey the annual morbidity rate amongst children originally positive was 4·3 per 1,000 in contrast to 1·4 per 1,000 amongst those originally negative (Jarman, 1955). D'Arcy Hart and his colleagues (1956) have pointed out that in the Medical Research Council's BCG trials children with strong positive reactions at the outset were four times more likely to develop tuberculosis in the next two to three years than those with weak reactions and one and a half times more likely to do so than those with negative reactions who were left unvaccinated.

Bentley (1955) regards the positive tuberculin reaction in very young children as of supreme diagnostic importance and attacks the conception that "infection but no disease has occurred". He recommends that all infected children under 2 years of age should be given a course of PAS and INAH irrespective of the presence, absence, or extent of radiological shadows and that antibiotics should be given at any age to recent converters. Not all clinicians will agree with this; it is mentioned to give point to the contention that tuberculin sensitivity is a phenomenon which can have valuable diagnostic significance.

Use of the Tuberculin Test for Limited Research Purposes

Recently Carpenter and others (1956) have used the results of tuberculin testing in a community as one amongst other methods of assessing the tuberculous infectivity of progressive massive fibrosis in coal-miners. This study showed that in homes where there is a man with PMF whose disease is progressing the percentage of Mantoux-positive children is unlikely to exceed by more than 10% the proportion Mantoux-positive from comparable homes but without this possible risk of infection. Miller (1953) carried out a similar study relating to pottery workers and found that the incidence of positive reactors amongst those whom it seemed might be particularly exposed to infection from workers with tuberculoconiosis was no greater than amongst those not so exposed.

All the ways described in this paper in which tuberculin sensitivity in man has been used in the fight against pulmonary tuberculosis surely demonstrate that it is, and remains, a really formidable weapon in the hands of epidemiologists and clinicians alike.

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Section of Orthopædics

President—E. STANLEY EVANS, C.B.E., F.R.C.S.

[*November* 6, 1956]

Osteoid Osteoma of the Transverse Process of the Fifth Cervical Vertebra.—F. GODSALVE WARD, F.R.C.S.

Peter F., aged 11 years.

At the age of 8 years he presented with a year's history of increasing pain in the neck which was rigid on examination. He was treated as a case of cervical caries with a Minerva plaster followed by a Robert Jones frame on account of subsequent spasm in the left hip. In January 1955 the lesion in the neck was explored and after removal of ivory hard bone a cherry red core was curetted which had the histological appearances of osteoid osteoma. The X-rays show the evolution of the tumour which had become painless by the time that the operation was done.

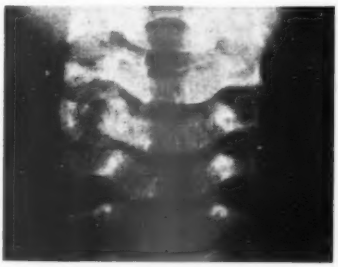


FIG. 1.—29.12.53.



FIG. 2.—10.12.54.

The last comprehensive survey of osteoid osteoma was by Golding (1954) who reported 178 cases from the literature of which 19 were in vertebræ, and added 20 of his own including 2 more vertebral cases. Jackson (1953) had found 217 in the literature with 19, presumably the same 19, in vertebræ, so the vertebral incidence is about 1 in 10 of all cases of osteoid osteoma. One of Jaffe's (1935) original 5 cases was in the spinous process of C7.

A special feature of some of the spinal cases has been the hypertrophic change in the adjacent joint first pointed out by Mary Sherman (1947) which may encroach upon the intervertebral foramen. One case in the vertebral arch of L2 reported by Fagerberg and Rudström (1953) presented just like a "disc sciatica" and Jackson's (1953) case in the arch of L8 was diagnosed only at operation for a supposed neurofibroma of the 8th dorsal nerve root. The case reported by Campos (1946) in the spinous process of C4 was first diagnosed as tuberculous and had a mild leucocytosis and an E.S.R. raised to 33 mm. (Westergren) in the hour but tuberculosis was later disproved by a negative Mantoux test.

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Two Cases of Sarcoidosis with Peripheral Joint Manifestation.—R. A. BREMNER, F.R.C.S., for P. H. NEWMAN, D.S.O., F.R.C.S.

Case I.—C. F., male, aged 40. Electrical engineer.

History.—First noticed swelling of the second toes of both feet in 1941, and a little later a discoloured swelling of his right cheek. Biopsy was carried out and a histological diagnosis of sarcoidosis made. Gold therapy was tried, but abandoned owing to the development of nephritis.

Subsequently he remained fairly well, apart from a complaint of persistent catarrh, until 1950, when his fingers began to swell and become stiff. This has gradually progressed over the past five years; the patient says more rapidly recently. Two courses of deep X-ray therapy to the hands were tried in 1950 and again in 1955 without improvement.

The patient came under the care of the Middlesex Hospital in September 1956. The main complaints then were of progressive swelling, stiffness, and clumsiness of his fingers, and of persistent catarrh, coupled with general malaise.

On examination.—The hands showed soft fusiform swellings of the fingers and thumbs, although the right thumb was relatively little affected, of such extent that a fist could not be made with either hand, and fine movements of the fingers were seriously impaired.

X-rays: Hands and feet showed typical bone changes of sarcoid; chest showed typical hilar lymphadenopathy.

Blood.—E.S.R. 8 mm. in first hour (Westergren). Hb 106% (15·4 grams%). W.B.C. 4,900: differential count normal. Serum calcium 9·3 mg.%. Plasma phosphate 3·5 mg.%. Total protein 8·3 grams% (albumin 4·1, globulin 4·2 grams%). Electrophoretic pattern normal.

Blood urea 37 mg.%. Mantoux reaction negative. Renal investigations and barium meal revealed no abnormality.

Biopsy of nasal mucosa positive for sarcoid.

Treatment and progress.—Prednisolone in a dosage of 5 mg. q.i.d. had been given for two weeks with marked improvement in finger function.

Case II.—T. P., aged 41. Electrical engineer. (Dr. Paul Strickland's case.)

History.—In 1948 a routine X-ray showed a bilateral hilar lung lesion suggestive of sarcoidosis. The patient was at that time symptom-free. In 1952 he developed a painful swelling of the proximal phalanx of the ring finger of his left hand, which gradually increased.

X-ray of the hand showed typical sarcoid bone lesions. (These changes have not altered during four years of observation in spite of marked improvement in the clinical picture.)

Blood: E.S.R. 5 mm. in first hour (Westergren). Serum calcium 10 mg.%. Total protein 7·7 grams% (albumin 4·5, globulin 3·2 grams%). Electrophoretic pattern shows an increase in the alpha-2 fraction. Mantoux reaction negative. Kveim test positive.

Biopsy of left axillary gland (1954) positive for sarcoid.

Treatment and progress.—In 1954 a course of ACTH was given for six weeks with slight benefit. In 1955 skin lesions on the hands developed. Cortisone orally was given for twelve months with improvement in the range of finger movement and diminution of the swelling. Some fading of the skin plaques also took place.

In June 1956 prednisolone in a dosage of 5 mg. q.i.d. was commenced with marked improvement. Reduced to 5 mg. t.d.s. on 1.8.56, and again to 5 mg. b.d. on 26.9.56.

Present condition.—Slight thickening of the soft tissues of the ring finger of the left hand, and faded remnants of skin plaques are visible on the dorsum, but a good fist can be made, and the maintenance dose of prednisolone, 5 mg. b.d., keeps up the good results. The patient does full work at his previous employment.

Lipoma Causing a Posterior Interosseous Nerve Lesion.—A. D. THOM, M.B. (for R. H. MAUDSLEY, F.R.C.S.).

Mrs. F., aged 47, a housewife, had since January 1956 noticed a progressive weakness of extension of the right thumb and fingers with some aching down the lateral aspect of the forearm.

On examination (7.8.56).—There was an almost complete right posterior interosseous nerve paralysis. There was $\frac{3}{4}$ in. wasting of the forearm and no obvious sensory changes. There was a diffuse palpable swelling present in the outer aspect of the antecubital fossa. There was no other relevant abnormality.

Investigations.—X-ray of elbow showed a radiotranslucency resembling a gas bubble, anterior to the neck of the radius. Blood and urine examinations normal. E.S.R. 12 mm./first hour (Westergren). W.B.C. 8,800. Hb 86% = 12·8 grams%.

A provisional differential diagnosis was made of: (1) Lipoma. (2) Neurofibroma.

9.8.56: As the paralysis was progressing an exploratory operation was undertaken

Through a Kocher's incision the posterior interosseous nerve was found stretched across a fatty mass deep to the supinator. The nerve was bluish in colour and appeared cystic and degenerate.

On reflexion of the supinator the mass appeared to be a lipoma closely applied to the head and neck of the radius and extending into the elbow-joint, where the mass was whiter and of a firmer consistence. On removing the mass the anterior surface of the neck of the radius was seen to be bare of periosteal covering and the rim of articular cartilage of the head had been eroded.

Histology.—Fibrolipoma.

Progress.—Rapid progressive recovery of the paralysed muscles.

Comment.—Peripheral nerve lesions due to lipomata are rare. In the 2 cases previously described in this area the lipoma lay in the substance of the supinator muscle (Campbell and Wulf, 1954; Richmond, 1953).

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An Unusual Patella.—G. O. TIPPETT, F.R.C.S.

A woman now aged 70, in 1940 fell on her left knee bruising it. She rested the knee for some weeks at home then resumed her employment as a part-time cleaner. Her knee has caused no trouble until the last few years when she considered that the patella had commenced to enlarge.



FIG. 1.

First seen June 1956; the patella was greatly enlarged, rough and irregular, nearly the size of an orange and fixed to the tibia so that the patella moved with the tibia in flexion. In spite of this she had a full range of movements and after a few physiotherapy treatments she had no pain and the power and function of the knee returned to normal. The X-ray showed gross enlargement of the patella with obvious old fragments of the original patella surrounded by a mass of new irregular bone formation suggesting an old comminuted fracture of the patella with much local hæmatoma formation which has slowly undergone ossification and moulded itself around the patella fragments (Fig. 1).

Undiagnosed Lesions of Both Tibiæ.—R. H. METCALFE, M.D., M.Chir., F.R.C.S.

J. S. Born 29.11.45.

21.6.55: Presented with a history of three weeks' pain and swelling in right knee. On examination knee was hot and slightly swollen but there was no fluid in the joint and movement was painless. X-ray: Increased density of upper epiphysis of right tibia, probably a form of osteochondritis (Ritter's disease)—may be a chronic inflammatory condition.

2.7.55: No complaint. 100% function.

18.8.55: Knee now definitely swollen; boy has a slight limp. Right upper tibial condyle is tender. Control X-ray: no change (Fig. 1). Also pain in left knee. Right ankle and big toe. X-ray showed nothing abnormal.



FIG. 1.



FIG. 2.



FIG. 3.



A



B

FIG. 4.

19.8.55: Admitted Queen Mary's Hospital for Children, Carshalton. Still has 100% function.

22.8.55: X-ray: In addition to sclerosis of upper right tibial epiphysis, there are abnormalities in lower poles of both patellæ suggestive of osteochondritis. Mantoux test negative in all dilutions. E.S.R. 30 mm. in first hour (Westergren). Treated on tip up bed with reduction of heat and swelling.

17.10.55: Walking in right patten-ended Thomas's caliper with raised left boot.

11.11.55: Control X-ray: Similar sclerosis has appeared in upper left tibial epiphysis. Still no change in associated metaphysis (Fig. 2).

19.12.55: Discharged home walking in right patten-ended caliper.

15.3.56: Control X-ray: Commencing rarefaction of metaphysis upper end of both tibiæ. This change supported diagnosis of bilateral osteochondritis upper tibial epiphysis (Ritter's disease).

17.5.56: Control X-ray: Condition in upper end both tibiæ slowly progressing. Half-inch lengthening right leg. Patten-ended caliper discarded.

5.7.56: Control X-ray: Upper tibial epiphyses appear to be re-vascularizing.

20.7.56: Control X-ray of knees: showed *for first time* an abnormality in right tibial shaft (Fig. 3).

Diagnosis: Syphilis. W.R. of boy and both parents negative.

14.9.56: Biopsy: Reticulosarcoma involving bone and periosteum.

19.9.56: Discharged home walking normally.

6.11.56: Case shown at Orthopædic Section, Royal Society of Medicine. The following possible diagnoses were made:

(1) Dual pathology. (*a*) Osteochondritis upper tibial epiphyses; (*b*) Sarcoma shaft right tibia. (2) Chronic low-grade infection. (3) Hodgkin's disease (Sir Thomas Fairbank). (4) Neurofibromatosis. (5) Myelomatosis. (6) Secondary to parathyroid tumour. (7) Melorheostosis.

14.11.56: Readmitted Queen Mary's Hospital for Children, Carshalton.

Blood count (16.11.56): Total W.B.C. 6,000. Neutrophils 59%, lymphocytes 32%, monocytes 8%, eosinophils 1%. Hæmoglobin 82% (12·1 grams %). E.S.R. 49 mm. in first hour.

Urine (15.11.56): Protein nil. Deposit: Amorphous phosphates.

Blood chemistry (16.11.56): Alkaline phosphatase 22 units. Calcium 11·6 mg./100 ml. Inorganic phosphorus 15 units. Zinc sulphate flocculation 15 units. Electrophoretic analysis of the serum shows a marked increase in gamma globulin. The calcium and phosphorus are also elevated. Marrow biopsy from ilium (15.11.56): No evidence of myelomatosis or neoplasm. Blood culture (15.11.56): No growth after three weeks' incubation. Right leg now one inch longer than left. Treated by three weeks' intensive penicillin.

11.12.56: E.S.R. 22 mm. in first hour.

17.12.56: Control X-ray (Fig. 4A, B) suggests consolidation of lesion of tibial shaft. Discharged home. Diagnosis still not known.

Rotational Dislocation of Atlas on Axis.—F. G. St. Clair Strange, F.R.C.S.

E. H., female, aged 21. Physical education student.

17.7.56: During a rag the patient fell and hurt her neck. Admitted with head held fully rotated to right. Pain and tenderness of upper cervical muscles. No neurological signs.

X-rays showed rotational dislocation of atlas on axis. No fracture seen.



Fig. 1.—X-ray showing lateral view of skull and atlas with almost exact antero-posterior view of axis and remainder of cervical spine. Both superior articular facets of the axis can be seen devoid of corresponding atlantal articulations.

Treatment: A gentle manipulation without anæsthetic, and head traction. 48 hours later: Plaster collar applied.

7.9.56: Plaster removed. Felt collar supplied.

5.10.56: Full range of movement present in neck.

Disorders of the Temporomandibular Joint.—J. L. HARRINGTON, L.R.C.P., M.R.C.S., L.D.S.

An analysis of the clinical aspects of 260 cases of disorders of the temporomandibular joint reveal that one or more of the following symptoms may be present: (1) Clicking (2) Locking, (3) Pain.

(1) *Clicking.*—This symptom when unaccompanied by locking or pain is of little significance and no treatment is usually necessary. It is often due to the anatomical shape of the glenoid fossa and eminentia articularis which allows an asynchronous movement of the head of the condyle with the meniscus. Self-inflicted trauma, such as yawning or biting hard food substances, will often produce this symptom which will become resolved in a few days with adequate rest of the joint. Should the patient complain of locking of the joint or pain, then attention must be given to faulty articulation of the teeth which is invariably present.

(2) *Locking.*—Limitation of movement may be severe and is often maximal on awakening; or slight when it may be accompanied by a swing of the mandible away from the affected joint on opening the mouth. This symptom is alleviated by correction of the dental abnormality.

(3) *Pain.*—Two types of pain can be differentiated: the one occurring in the region of the joint and accompanied by local tenderness, or referred to any branch of the trigeminal nerve, while the other type manifests itself as a deep dull ache in the facial musculature.

In the first type, the pain invariably occurs on the same side of the face to which the mandible moves on eccentric excursions. The essential factor is abnormal tooth contacts which cause deviation of the mandibular arch during its path of closure. Radiographically there may be no evidence of alteration or loss of joint space, but occasionally the condyle is forced posteriorly and there is then diminution of joint space between the condyle and the tympanic plate.

Pain, however, has no direct relationship to this malposition, but is probably due to the stretching or torsion of the lateral ligaments and capsule around the joint (*see* Fig. 1).

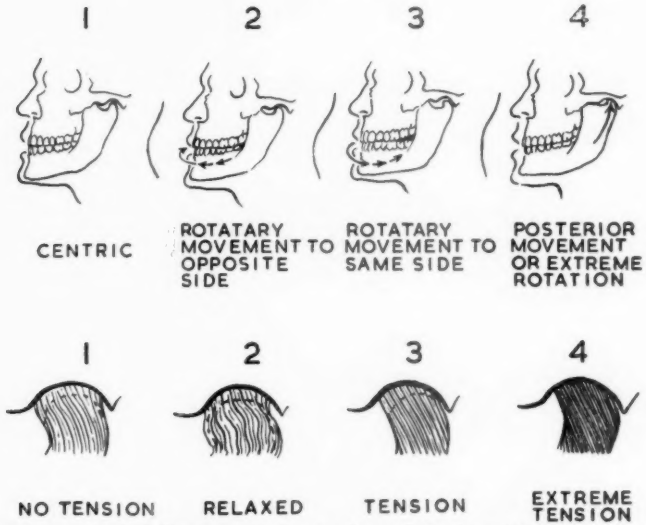


FIG. 1.—Diagrams 1, 2, 3 illustrate varying tensions of the lateral ligament of the mandible under normal masticating movements. Diagram 4 exhibits stress when abnormal dental contacts are present. Clinically tenderness can be palpated via the external auditory meatus or in the pre-auricular region.

Treatment consists in the correction of the dental abnormality, when the painful symptoms rapidly disappear.

In the second type, the patient complains of a dull deep muscular ache. When the pain is unilateral, the causative factor is usually abnormal tooth contacts. Not infrequently, however, there is loss of vertical height in occlusion due to loss of teeth or alveolar bone, when the pain is bilateral. This is noticeable in the masseter, digastric and anterior fibres of the temporalis, which muscles may also be tender to palpation (Fig. 2).



A B

FIG. 2.—A, A case of bilateral pain and tenderness in both masseter and digastric muscles due to loss of posterior teeth, resulting in the overclosure of the mandible. B, Establishment of oro-facial harmony by insertion of dental prosthesis with relief of symptoms.

Skeletal asymmetry may cause the mechanism of mastication to become inco-ordinated, and the line of occlusion may slope definitely from one side of the face to the other. This may produce similar signs and symptoms to those already described.

Whether as a result of a skeletal abnormality or an acquired fault in occlusion, the muscles of mastication are hyper-activated as a result of the patient endeavouring to maintain some kind of functional mastication. This muscle hyper-activity will often lead to muscle fatigue which is characterized by deep pain and tenderness in the muscles of mastication. In these cases, localized pain around the temporomandibular joint may not be present.

With this syndrome it has been found that the facial nerve may also be involved and, rarely, the muscles of facial expression may be affected with apparent facial nerve paresis. Electrical stimulation of the VII nerve, however, as it crosses the posterior border of the ascending ramus of the mandible, produces a greater excitation of these muscles compared with the normal side (in comparison with Bell's palsy where the response may be diminished or absent).

Correction of the dental disharmony reduces this increased excitation, relieves the pain, and within fourteen days of treatment both sides react equally to the same stimulus.

It is considered that the deep pain and tenderness are the result of muscle fatigue and not of muscle spasm since electromyographic records taken of these cases do not show increased frequencies to the point indicating spasm, e.g. 200 per second.

An explanation is at present impossible. There are definite links between all the branches of the facial nerve and corresponding branches of the trigeminal nerve, and the key to the involvement of both these nerves in the syndrome would appear to lie here. Whether these connexions contain fibres running from the facial to the trigeminal, vice versa or both ways, is unknown. One possible thought is that occasionally throbbing is complained of with a severe pain in the joint, and it may be that the basic cause is a vascular one fired off by impulses from the temporomandibular joint which is innervated not only by somatic fibres but by autonomic fibres also. Beyond this hypothesis it is not possible to go.

Arthrogryposis Multiplex Congenita.—R. H. SEWELL, Ch.M.

Male child, aged 2½ years, the elder of two children, the younger being normal. Both parents show no abnormality nor is there any family history of skeletal or muscular disease.

At birth, the deformities present were:

(1) Ulnar deviation and palmar flexion of the hands.

(2) Fixed extension deformities of the elbows and adduction deformities of both shoulders.

(3) There was a severe bilateral talipes equino-varus.

The feet have been corrected with difficulty by manipulations and strapping and later, Denis Browne splints. He walked at 18 months. Despite repeated manipulation and splinting, the elbows remain in full extension.

Opinions were sought on the future treatment of this child. The Meeting was of the

general opinion that no surgical treatment was advisable, at least at present, although cases of successful Clarke's transplant in older children with an adequate pectoralis major were quoted.

? Giant Cell Tumour of Neck of Radius.—R. H. V. HAFNER, F.R.C.S.

W. O., aged 64. Paper maker.

History.—Patient hurt his right elbow at work in April 1956. X-ray showed no bony injury but revealed a multilocular cystic tumour occupying the proximal end of the radius at the junction of the shaft and the neck (Fig. 1). The cyst was expanding the bone and contained small nuclei of bone. The differential diagnosis was thought to lie between the following: (1) Enchondroma. (2) Osteitis fibrosa cystica (localized). (3) Osteoclastoma.

The pain and stiffness of the elbow which had followed the injury rapidly subsided and within a few weeks the joint was clinically normal.

Check X-ray of the right elbow taken in July 1956 showed no change from the previous films (Fig. 2).



FIG. 1.—X-ray of elbow, postero-anterior view.



FIG. 2.—X-ray of elbow, lateral view.

The patient is doing a heavy job and is entirely free from symptoms.

The questions before the Meeting were: (*a*) Diagnosis. (*b*) Should the tumour be excised because of the possibility of malignant change?

Past history.—Nine years ago, the patient injured his right elbow and was said to have sustained a fracture of the head of the right radius. No records are available.

A medico-legal point has arisen in this case because of the possibility that this cystic tumour had resulted from the injury nine years ago.

POSTSCRIPT (March 1957).—Patient at work and symptom-free. X-ray appearances are unchanged.—R. H. V. H.

Result of Removal of Right Lunate Bone (Semilunar) Eighteen Years Ago.—W. E. TUCKER, F.R.C.S.

Male, aged 42.

February 1938: Injured right wrist playing hockey.

First seen on 1.4.38 with X-rays which showed dislocation of the lunate bone.

As attempts at manipulative reduction failed, an open operation was performed and the bone removed.

Since then has been playing county hockey, hammer throwing and weight lifting. Has full range of right wrist movement and only has an occasional twinge.

The following cases were also shown:

Sequelæ of a Fractured Head of Radius.—G. O. TIPPETT, F.R.C.S.

Non-union of Ulna.—J. H. MAYER, F.R.C.S.

(1) Case Illustrating Use of Walking Caliper in Plaster Boot: Fracture of lower third of the right tibia and fibula. **(2) Case Illustrating Use of Home-made Removable Walking Caliper:** Arthritis of the right knee-joint—unknown origin.—W. E. TUCKER, F.R.C.

Section of Proctology

President—RONALD W. RAVEN, O.B.E., T.D., F.R.C.S.

[*January* 9, 1957]

Carcinoma of Pelvic Colon. Secondary Deposit in Left Ureter Simulating a Primary Tumour. Left Hydronephrosis.—H. R. THOMPSON, F.R.C.S.

Mrs. E. S., aged 47.

23.3.55: *Laparotomy* for acute bowel obstruction due to growth at pelvi-rectal junction. Transverse colostomy.

1.4.55: *Sigmoidoscopy* and biopsy showed an infiltrating adenocarcinoma at 15 cm.

7.4.55: *Laparotomy.*—"Growth infiltrating the abdominal wall, uterus and small intestine, and was considered inoperable." Section of a hard nodule of tissue from the right broad ligament showed it to be adenocarcinoma.

10.7.56: Patient remained well until readmitted to hospital with abdominal pain and vomiting which responded to colostomy wash-outs; the pain, however, persisted.

22.8.56: First attended St. Mark's Hospital as a thin, dehydrated, ketotic woman with a gross small bowel obstruction. Hiccoughing following continuous vomiting for fourteen days.

Laparotomy.—Findings: (1) Obstruction due to matted coils of small intestine firmly adherent to growth in recto-sigmoid bowel. (2) No secondary deposits in the liver. (3) Solid tumours of right and left ovaries. (4) Rigid, distended appendix. (5) Left hydronephrosis with nodule in lumen of left ureter at pelvic brim.

Operative procedure: (1) Resection of pelvic colon and upper rectum with 4 ft. of adherent small intestine. (2) Pan-hysterectomy with appendages. (3) Left nephrectomy for left hydronephrosis and hydro-ureter secondary to ureteric growth at pelvic brim. (4) End-to-end colo-rectal anastomosis.

Stormy post-operative convalescence due to partial breakdown of anastomosis and pelvic abscess. Discharged eight weeks after operation.

27.11.56: Readmitted. Stricture at anastomosis dilated.

19.12.56: Intraperitoneal closure of colostomy.



Pathological report.—"(1) Ulcerating constricting adenocarcinoma of rectosigmoid. (2) Secondary deposits in both ovaries. (3) Secondary deposit in appendix. (4) The tumour in the ureter was a secondary deposit of adenocarcinoma. There was permeation by adenocarcinoma of a moderately sized vein close to the tumour in the ureter. There was obvious invasion of veins in sections of the primary growth."

Comment.—The case is of interest for: (1) the urological aspect; (2) the prognosis and operability; (3) the diagnosis.

(1) *Urological aspect.*—Most surgeons, on finding a left hydronephrosis and left hydroureter at operation for advanced carcinoma of the pelvic colon, would correctly assume this to be due to direct involvement of the ureter by the colon growth. This was the assumption in the case reported until it was found that the colon growth lifted easily off the ureter without dissection, revealing a hard nodule within the lumen of the ureter just below the pelvic brim. The nodule was about 2 cm. long and was apparently malignant tissue (Fig. 1). Was this an associated primary carcinoma

FIG. 1.—Hemisected left kidney and ureter seen from behind, showing ureteric tumour—a secondary deposit of colonic adenocarcinoma.

of the ureter, or a secondary deposit from the primary colon growth, and, if so, what was its mode of spread to the ureter?

Histological examination showed that the ureteric tumour was a deposit of colonic adenocarcinoma. From the ease of separation of the primary colon growth from the ureter and the appearance of the nodule and the ureter it is unlikely that the spread was by direct extension. A clue to the possible spread was provided by the finding of a peri-ureteric vein adjacent to the ureteric tumour filled with adenocarcinoma and it is suggested that the secondary deposit developed in the lumen of the ureter from retrograde venous spread.

Kontoff and Hershman (1954) reported a case of primary transitional cell carcinoma of the LEFT ureter being treated five months after a RIGHT hemicolectomy for carcinoma of the ascending colon. They stated that since Rayer (1841) in France first reported a case of primary carcinoma of the ureter, there have been 312 such cases reported but that none of these cases was associated with another primary malignancy.

The treatment of this urological complication arising during the resection of a carcinoma of the pelvic colon was a matter of expediency. As the right kidney and ureter were normal, it was considered that a left nephro-ureterectomy was preferable to reconstructive surgery as the operation had already lasted three and a half hours.

(2) *The prognosis and operability.*—I think it is agreed that fixity of a growth as assessed at clinical examination should not condemn a patient as inoperable. Everyone is familiar with the growth that appears hopelessly fixed, clinically, being quite easily removed at operation and most give their patients the benefit of a trial dissection. If this fails a colostomy should be performed and the case reviewed every three months. In larged fixed growths after a colostomy the patient usually enjoys a period of nine to twelve months of good health and during it the surgeon should elect to do a second laparotomy. Sometimes he will find that the case has become operable.

Dukes (1949) refers to the paradoxical situation that beyond a certain limit in size, the larger the tumour the less likelihood there is of metastases and, presumably, the better the prognosis.

Cooke (1956) discussed advanced carcinoma of the colon with emphasis on the inflammatory factor. He gave examples of 14 cases of extended resections for carcinoma of the colon where both the quality and length of life were improved and extended in patients who might have been left as inoperable.

(3) *The diagnosis.*—It is interesting that the patient was originally admitted to hospital in March 1955 suffering from an acute abdomen and diagnosed as appendicitis. Laparotomy, however, revealed a distended cæcum and a large bowel obstruction due to a constricting growth in the pelvic colon. A distended cæcum can simulate appendicitis, but seventeen months later the appendix was grossly pathological, it was removed, and on section its lumen was full of secondary adenocarcinoma.

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"Weaver's Bottom" (Ischial Bursitis).—DAVID BAILEY, M.Chir., F.R.C.S. (for IAN TODD, M.S., F.R.C.S.).

History.—W. E. B., male, aged 70, attended St. Mark's Hospital in September 1956. In 1921 a right-sided ischial bursa was excised at St. George's Hospital. He had remained well until August 1956 when he noticed a swelling in the left ischial region and a sinus developed in the right-sided scar. Weaver's bottom was diagnosed and X-rays demonstrated rarefaction of both ischial tuberosities with considerable irregular new bone formation. By November 1956 the left-sided bursitis became acute; patient transferred to University College Hospital.

Examination.—Right ischial region: Scar of previous operation with discharging sinus and recurrence of bursa. Left ischial region: Acutely inflamed bursa 7 cm. in diameter.

Operation.—13.11.56: Left ischial bursa excised intact with ellipse of overlying skin. A hæmatoma formed; it was drained; healing was slow.

Specimen.—Ovoid cyst 7 × 5 × 4 cm.; wall thick (0·25–1 cm.) with polypoid projections into lumen, which was filled with sterile, gelatinous, yellow fluid. "Chronic bursitis—no evidence of tuberculosis".

Comment.—This condition is rare to-day and is usually attributed to trauma by prolonged sitting, &c. Rowing may have been an ætiological factor in this case.

Intussusception of Appendix Simulating a Carcinoma of the Cæcum.—FRANK FORTY, F.R.C.S.

M. B., female, aged 61.

History.—Attacks of lower right colicky abdominal pain for one month, latterly with vomiting. Bowels acted normally; once loose, contained altered blood.

On examination.—Mass in right iliac fossa, mobile, slightly tender but no guarding. Pre-operative diagnosis: Carcinoma of cæcum with subacute intestinal obstruction.

Operation.—Mass in cæcum; no enlarged lymph glands; no secondaries in liver. Right hemicolectomy. Uneventful recovery.

Report (Fig. 1): The specimen consists of the terminal 5 cm. of ileum, the cæcum, appendix and 21 cm. of colon. The appendix is intussuscepted into the cæcum, and is grossly thickened. Its lumen is almost obliterated with cheesy material, but no tumour is seen.

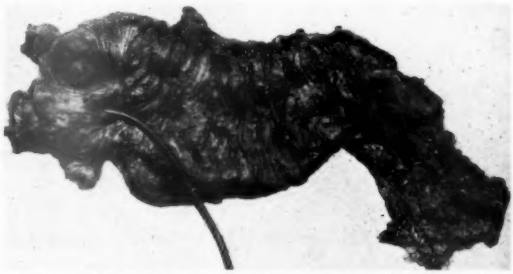


FIG. 1.—The operation specimen opened to show the intussuscepted appendix; ileo-cæcal valve shown by rubber tube.

Histology.—Section: No tumour, only the acute inflammatory changes associated with the intussusception, the muscle coats being particularly affected.

Comment.—About 100 cases of intussusception of the appendix have been reported (Fraser, K., 1943, *Brit. J. Surg.*, 31, 23).

Ætiology: Concretions, tumours, mucoceles, enlarged glands, worms, have been associated conditions. In many cases, as also in this case, no causative factor was found.

Symptomatology: Intussusception of the appendix occurs at all ages. It runs a chronic course extending over weeks or months. Severe colicky pain and a palpable mass in the right iliac fossa are constant findings. In a minority blood or mucus is passed *per rectum.* An X-ray after a barium enema generally reveals a filling defect in the cæcum. The usual diagnosis is acute appendicitis or carcinoma of the cæcum.

Treatment.—Appendicectomy with or without preliminary reduction of the intussusception, or hemicolectomy if a growth is suspected—or if the intussusception has become compound and includes cæcum, ileum or ascending colon.

Stenosed Segment of Descending Colon Associated with Trauma.—RUPERT CORBETT, M.Chir.

Specimen shown to the Section for diagnosis was the stenosed segment due to trauma or to an underlying condition such as regional colitis (Crohn's disease).

Male, aged 36—labourer.

17.3.56: Fell from height of 14 ft. and admitted as an emergency with abdominal pain, at 1 p.m. Had fracture of 8–9–10–11 left ribs and of left ilium. Abdominal pain persisted. At 6 p.m. glycerin suppositories gave a fæcal result; no blood in motion or in urine. Left-sided pain persisted. Condition satisfactory. During night passed blood *per rectum.* Blood pressure 90/60. Given pethidine—improved.

18.3.56: Much improved. Still blood *per rectum.* Urine clear.

22.3.56: Bleeding subsided. W.B.C. 21,000. Abdomen soft though tender on left side.

30.3.56: *After eight days* stools became offensive with pus. W.B.C. dropped to 6,000.

7.4.56: *One week later* improved; tender in left iliac fossa. Passed 2–3 motions daily.

21.4.56: *Five weeks after admission*: Anæmic; Hb 76%; transfused.

12.5.56: *Eight weeks after admission.* Discharged. Improved. Stools normal consistency though narrow and ribbon-like. Bowels open 2 to 4 times daily.

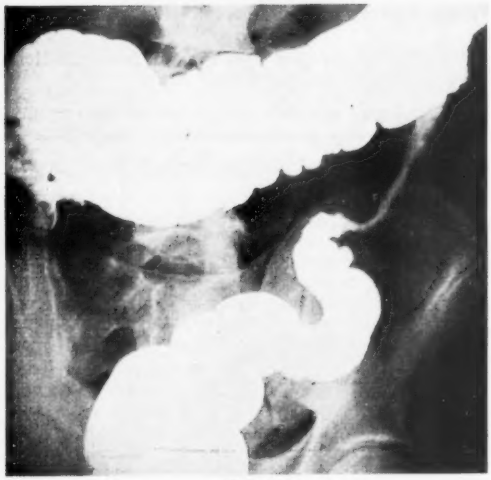


FIG. 1.



FIG. 2.

X-rays: Barium enema showed free passage as far as cæcum; descending colon was narrow (Fig. 1).

8.11.56: Readmitted for operation.

13.11.56: *Resection of descending colon* twelve weeks after injury. 12 in. of colon resected and end-to-end anastomosis. Specimen injected for blood supply (Fig. 2). Mid-colic and left colic arteries were tied. No rupture was detected.

29.11.56: Discharged.

21.12.56: X-rays—Bowel normal, five weeks after operation.

I am indebted to Mr. J. D. Griffiths for the injection of the sigmoid. He has been working on the subject of blood supply to the colon. The resected sigmoid did not reveal any arterial block or damage. I think that the condition could have been caused by trauma, although the interval between it and the established diagnosis was about eight weeks.

Pathological report (22.11.56).—*Macroscopic:* The specimen of colon is 29 cm. in length after fixation, with the attached meso-colon and omentum adherent. The vessels had been injected with opaque blue dye. The colon is shrunken, its lumen is reduced throughout and its wall thickened due partly to folding of the muscularis. The mucosa is abnormal, but the lining is so discoloured that it is impossible to say whether ulceration is present or not.

Histology: Sections of the colon showed inflammatory changes in all coats. The mucosa shows low-grade active chronic inflammation and there is evidence of extensive regeneration. No ulceration is apparent. The submucosa shows fibrosis and scarring—especially superficially where the fibres of the muscularis mucosæ are widely separated by fibrous tissue. There is fibrous thickening of the serous coat and occasional small groups of inflammatory cells in the outer part of the wall. In these sections there is no apparent abnormality of the vascular supply.

Seven lymph nodes from the meso-colon show only non-specific reactive changes.

The appearances are somewhat suggestive of Crohn's disease though proof of this is lacking.

In the discussion **Mr. R. V. Cooke** said he thought that the changes which had taken place could be explained by a very extensive traumatic thrombosis of the bowel wall, subsequent on a severe contusion. This is supported by the passage of blood and pus from the bowel. Subsequently fibrosis and narrowing of the lumen followed.

Potassium-secreting Tumour of the Colon.—CYRIL COOLING, F.R.C.S. and DAVID MARRACK, M.D.

This title was given to a large villous tumour of the sigmoid colon because of the vast secretion of potassium associated with the lesion, which led to a serious deficit in the body potassium.

A female, aged 35, attended the Gordon Hospital in 1947, complaining that she had been passing water through the rectum for five years but blood had been present only at the onset. The symptoms had started six months after a normal, but rapid, labour.

Every morning she passed a loose motion mixed with fluid followed by a formed stool, and for the rest of the day passed this watery fluid with every micturition.

Sigmoidoscopy and barium enema at that time failed to reveal any evidence of tumour or vesical fistula and the diagnosis was mild colitis. Medical treatment and colonic lavage provided some improvement. The symptoms did not unduly worry her.

In 1955 she attended the Gordon Hospital, and was admitted for investigation under Mr. S. O. Aylett. For a month she had felt ill with vomiting and abdominal discomfort, and for four days no fæcal matter had been passed. The rectal fluid continued to be poured out at 4–6 pints per day.

Examination revealed a heavily loaded colon but a rectum containing only fluid. The clinical impression was that she had subacute intestinal obstruction.

	m.eq./l.		mg./100 ml.
Serum		Serum	
sodium ..	120	calcium ..	10·3
potassium ..	2·2	Blood urea ..	97
chlorides ..	80		
HCO_3	27		

During the first six days intravenous electrolytes were given as follows:

	Pints
2N saline	12·5
N/5 saline and glucose ..	5
KCl (40 m.eq./l.) ..	8
M/6 sodium lactate ..	2

By mouth she received 144 grams of potassium citrate. It was found difficult to improve the serum electrolyte values in spite of this therapy. She complained of weakness and diplopia, and had episodes of tingling and numbness of the hands and occasional attacks of carpopedal spasms, a phenomenon which may occur during potassium replacement therapy with an existing low serum and total body potassium, yet a normal serum calcium (Fourman, 1954).

A barium enema examination revealed a fluffy outline in the distal part of a long sigmoid colon and sigmoidoscopy showed a granulomatous polypoid mass at 15 cm. A left hemicolectomy was performed for a palpable tumour of the sigmoid colon (Fig. 1). This



FIG. 1.—Macroscopic appearance of the villous tumour of the sigmoid colon removed by left hemicolectomy.

was examined by Dr. George Lumb who found an enormous encircling cauliflower tumour mass covering 11 cm. of colon but bounded by normal mucosa. Histological examination showed a papilliferous tumour with no evidence of malignancy but very active mucus-secreting goblet cells present.

Since removal of the tumour she is well and the serum electrolyte values have been normal.

Gabriel (1952) pointed out the difficulty of diagnosis of these soft impalpable, pale tumours but he considered that most of them would show some malignant change on serial section; a view endorsed by Swinton, Meissner and Soland (1955) who found such a change in 31·4% of their series at the Lahey Clinic. On these grounds it would appear that a radical approach in treatment is justified, a view expressed by Mr. Gabriel and giving excellent results.

In this case symptoms of electrolyte imbalance were present. It is known that severe fluid loss from the rectum as in gastro-enteritis may produce a similar condition, a phenomenon not previously recorded in association with villous tumours.

Electrolyte estimations of the simultaneously collected urine and rectal fluid on the third day after admission were:

	Urine m.eq./l.	Rectal fluid m.eq./l.
Sodium ..	0·5	122
Potassium ..	2·5	25

The significant facts are:

(1) The urine values approach the minimal possible level of both sodium and potassium which precludes potassium loss from other renal and steroid disorders.

(2) If the rectal fluid were a simple transudate the sodium/potassium ratio should be comparable to that of the serum.

(3) The tenfold increase in potassium over sodium values in this fluid can only be accounted for by selective reabsorption of sodium, urea, phosphate, chloride, calcium, phosphatases or by active secretion of potassium. It cannot be proved which occurred but as colonic mucosa is believed to secrete potassium under normal circumstances the vast increase in epithelial area in this tumour may account for this loss.

(4) Chronic loss of potassium presumably occurred over thirteen years. Signs and symptoms developed following one month of intermittent nausea and vomiting which probably reduced the potassium intake and further upset the intake/output balance of potassium.

(5) During potassium replacement therapy she developed tetany with full *main d'accoucheur* and Chvostek sign when the serum calcium and alkali reserve were normal. It was *not* relieved by calcium gluconate intravenously.

(6) All the serum electrolyte abnormalities corrected themselves and remained normal after removal of the secreting tumour.

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Section of Dermatology

President—Louis Forman, M.D., F.R.C.P.

[*November* 15, 1956]

Tuberculous Glands with Skin Involvement.—S. P. Hall-Smith, M.D., M.R.C.P., and J. McMurray, M.D.

A. W., aged 72.

History.—Six months ago, following right-sided sore throat, he developed swelling of right pre-auricular region. Three months later the swelling discharged pus, and soon after the surrounding skin became inflamed and reddened. During the same period further glands around the angle of his jaw on the right side, adjacent neck and supraclavicular area were involved. Before being referred for dermatological advice it was thought that he was suffering from a pyococcal infection and he was treated with Aureomycin ointment and intramuscular penicillin.

Examination.—The right cheek was covered by a diffuse erythematous papulo-pustular eruption. Over the pre-auricular area there was a prominent raised, infiltrated swelling; three discrete, cystic reddened swellings ran round angle of jaw; these have pointed and discharged pus. A palpable chain of glands extended from the right ear to right supraclavicular region. A small punctate ulcer could be observed between the anterior and posterior faucial pillars on the right side.

Investigations (17.10.56).—Hb 16·1 grams% (109%). W.B.C. 11,000 (polys. 80%, lymphos. 12%, monos. 8%).

Film: Red cells, leucocytes and platelets all appeared normal.

E.S.R. (Wintrobe) 31 mm. in one hour. (Normal 0–9 mm.)

26.10.56: *Swab:* A few pus cells and Gram-positive cocci seen. The culture gave a small growth of *Staphylococcus aureus*, coagulase +ve. Sensitive to erythromycin and Chloromycetin; resistant to penicillin, Aureomycin, Terramycin and streptomycin. *Mantoux test*, 0·1 c.c. 1/10,000 tuberculin: Positive (moderate reaction).

X-ray chest (15.10.56): Both costophrenic sulci clear. The heart and mediastinal shadows were normal and the lung fields clear.

Beard hairs: No fungus or pathogenic yeast isolated.

Biopsy of skin of right cheek, 17.10.56 (Dr. J. McMurray): This showed chronic inflammatory reaction of tuberculous type. No acid-fast bacilli were seen. There was also a pyogenic inflammatory reaction. Culture of the skin lesions gave a pure growth of *Staphylococcus aureus* (coagulase +ve).

25.10.56: A lymph node in the upper right cervical group was removed. This showed a tuberculous reaction with acid-alcohol-fast bacilli in the lesions. There was moderate caseation. Appearances resembled those seen in primary lymph gland tuberculosis in children. Some weeks later a culture of pus from fluctuant swelling below the skin lesion gave a growth of tubercle bacilli. It is not possible, at the moment, to say whether this is a human or bovine type.

Comment.—The findings are consistent with a primary tuberculous complex arising from the right tonsil involving the right upper cervical lymph nodes. The explanation for the skin lesion may lie in the probable lymph blockage with retrograde extension upwards from the infected lymph nodes. The localized skin œdema may have rendered atypical the appearances of the skin tuberculosis and also increased the possibility of secondary infection by *Staphylococcus aureus*.

Other possibilities, however, could be a primary senile tuberculosis either of right tonsil with lymphatic gland involvement and spread upwards and downwards, or of right lung with spread to hilum up the right paratracheal lymph glands and to involvement of right cervical group. This point may be clarified by subsequent investigation.

Dr. C. D. Calnan: I think the important thing in this case is the glands. The man is 72 and Rich (1951), in his book on tuberculosis, mentions this senile variety of tubercle in which the symptoms, signs, and the clinical course are different. Resistance to the organism changes in old age. I have seen a similar problem in an elderly patient with a big mass of glands at the neck, believed to be carcinomatous. At autopsy the mass was found to be tuberculous and, in addition, she showed other findings of senile tuberculosis with involvement of unusual organs such as the spleen.

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POSTSCRIPT.—Two weeks after the patient was shown at the meeting (29.11.56) he developed pyrexia, consolidation and probable collapse of the lower lobe of the left lung. It was thought by a consultant chest physician that he had active tuberculous glands in the mediastinum, one of which had ulcerated into his left lower lobe bronchus. It was suggested that if this gland was situated behind the left auricle, it would not be seen on X-ray and would also explain the patient's sudden development of auricular fibrillation. The patient's general medical and skin condition has improved with streptomycin, PAS and isoniazid. At present he is reluctant to be admitted to hospital for further investigation.—S. P. H.-S.

Acanthosis Nigricans.—P. J. HARE, M.D., M.R.C.P.

Married woman aged 42.

Gynæcological history.—1938: Toxæmia of pregnancy. Posterior occipital presentation, necessitating manual rotation and forceps delivery. 1943: Consulted gynæcologist for vaginal discharge: cervical erosion cauterized. 1950: Mild prolapse observed but cervix reported normal then and in 1954. 1956: Induration of cervix detected in August; cervical biopsy showed anaplastic carcinoma and radium was applied. Cervical lesion estimated at not more than one year's duration.

Dermatological history.—1942: Onset of discoloration of the skin of the sides of the neck and elbow folds. 1947: Seen by Dr. I. Martin-Scott who suggested a differential diagnosis of acanthosis nigricans or pseudoxanthoma elasticum. At that time the clinical changes consisted of tiny pigmented papules varying in colour from sand to deep brown, running in lines between the normal skin furrows of the axillæ, elbow folds and the sides of the neck. There was no atrophy or telangiectasia. Mouth and vulva normal. Biopsy showed a lymphocytic infiltrate in the dermis, with pigmented melanophores and colloid blocks, forming tiny papules with a thinned epidermis. Dr. W. Freudenthal stated that the histological features excluded the diagnoses suggested and that atrophic lichen planus seemed probable. At some time the likelihood of poikiloderma atrophicans vasculare must have been suggested and the case was shown with this diagnosis at the International Congress of Physicians in 1947.

1956: The patient thinks that the skin condition remained unchanged until a few months before entering hospital for the radium treatment. Pigmentation then increased and spread to parts previously unaffected. At that time she felt well apart from backache and a vaginal discharge: she was not suffering from fatigue, loss of weight or abdominal symptoms. She is now going downhill rapidly.

Examination.—The skin of the exposed parts is slightly dusky and both surfaces of the hands and fingers are horny. The palms show scattered pigmented spots but the palmar creases are not pigmented. In the axillæ and umbilicus there are slightly warty slate-coloured patches. The sides of the neck and the folds of the elbows are pigmented. The vulva is brownish-black and is crowded with closely set papules and warty growths. A few of the latter are scattered irregularly on the face, trunk and limbs. The roof of the mouth shows leukokeratosis. No pigmentation of the oral mucosa.

Investigations.—Plasma electrolytes normal. 17-ketosteroid excretion 6·8 mg./twenty-four hours (normal). Blood pressure 140/86. Biopsy from skin of pubis (8.11.56): Consistent with acanthosis nigricans.

Discussion.—There is histological evidence that she had poikiloderma in 1947, but, with the exception of pigmentation, no changes characteristic of this disorder have appeared. If she genuinely had poikiloderma, is there any significant connexion with the later development of acanthosis nigricans?

Dr. R. M. B. MacKenna: She shows very well typical changes on the palms, a matter which most of the literature does not emphasize. It seems to me that when in doubt as regards lesions in the armpits, if in the early stages one can find a velvety thickening of the palms, which proceeds to the stage shown in this patient, it is a very considerable aid to diagnosis. I do not think this change happens in all cases of acanthosis nigricans but when it occurs diagnosis is facilitated.

Necrobiosis Lipoidica.—P. J. HARE, M.D., M.R.C.P.

Married woman aged 43.

Family history.—No diabetes mellitus.

Past history.—Bronchiectasis since childhood. Lobectomy in 1949. Cough persists.

History.—Skin lesions for two years. Tender red nodules have appeared on the thighs and shins. These become flattened and painless after some months. Varicose veins for years but no phlebitis.

Examination.—Obese. B.P. 110/70. All peripheral pulses present and of good volume. Fundi normal. Varicose veins in both legs. No œdema or induration.

On both shins there are confluent areas of redness with yellowish centres and a glazed telangiectatic surface. On the left shin there is also a more discrete area 4 cm. in diameter with the same general appearance but with a distinctly raised narrow border. On the left thigh there is a slightly raised tender red area about 3 cm. in diameter.

Investigations.—Urine: no reducing substances. Fasting blood sugar and glucose tolerance test normal. Blood cholesterol 269 mg./100 ml. Mantoux test positive 1 : 1,000, negative 1 : 10,000.

Plethysmography (legs): high resting rate of blood flow and normal response to ischæmia.

X-rays.—Limbs: no calcification of blood vessels. Chest: changes corresponding to results of right lower lobectomy. Lung fields otherwise normal.

Biopsies.—(1) From a recent lesion: perivascular accumulations of histiocytes, epithelioid cells, giant cells of Langhans and foreign-body type, plasma cells and lymphocytes. No necrobiosis of connective tissue. Vessels normal.

(2) From an old lesion: the same inflammatory changes to a lesser degree and with fewer giant cells. In addition there are large areas of necrobiosis with early fatty change: there is fibrosis and occlusion of small arteries.

Two lesions have been treated by injecting hydrocortisone suspension into them, with cosmetic improvement.

The case is shown because it suggests that the early stage of necrobiosis lipoidica is inflammatory and not necrobiotic. Miescher's "granulomatosis disciformis" may in some instances represent this histological stage. Another point is the presence in the same patient of two types of mature lesion which have been thought characteristic of necrobiosis lipoidica in the diabetic and non-diabetic respectively.

The following cases were also shown:

Chronic Œdema of Hand—For Diagnosis.—Dr. W. D. FLETCHER and Dr. A. JARRETT.

Tuberculoid Leprosy.—Dr. W. H. JOPLING (for Sir GEORGE MCROBERT).

Recurrent Non-scarring Granuloma of Face for Diagnosis.—Dr. C. H. WHITTLE, Dr. A. J. ROOK, Dr. J. L. MOFFATT and Dr. R. A. DAVIS.

Kerato-acanthoma of the Lower Lip (Red Margin).—Dr. C. H. WHITTLE and Dr. R. A. DAVIS.

Pemphigoid.—Dr. M. WITHAM (for Dr. W. N. GOLDSMITH).

Dermatitis Herpetiformis.—Dr. W. FRAIN-BELL (for Dr. R. T. BRAIN).

(1) **Norwegian Scabies.** (2) **Familial Macular Pigmentation and Nerve Deafness in (a) Mother and Small Child, and (b) Unrelated Adult Male.** (3) **Acne Conglobata.**—Dr. I. MARTIN-SCOTT.

Ectopic Cutaneous Schistosomiasis.—Dr. H. HABER and Dr. J. COWLEY.

Ichthyosiform Erythroderma (Brocq).—Dr. H. WILSON and Dr. H. HABER.

Disseminated Granuloma Annulare.—Dr. PETER SMITH.

A paper on **Chronic Liver Disease as a Cause of Pruritus** was read by Dr. J. R. K. PREEDY.

[*December* 20, 1956]

Melanosis.—D. I. WILLIAMS, F.R.C.P.

B. G., aged 29. Occupation—shorthand typist.

History.—In February 1954 she noticed brown patches on the forehead and cheeks. Since this time these have spread slightly on to the neck and *pale* areas have appeared within the brown patches. The condition becomes more obvious during the summer months and less noticeable in the winter. She has never taken arsenic in any form or used any preparations containing silver or mercury. She has continued to use her face powder and cream without any noticeable effect on the pigmentation.

Past history.—No previous skin trouble. Asthma in 1949—none recently.

Examination.—Scattered over the forehead, cheeks, and upper parts of the neck there are areas of macular pigmentation, showing both a diffuse and follicular pattern. Intermingled with these pigmented patches are a number of rounded pale areas.

Investigations (right side of neck).—The section shows numerous chromatophores in the superficial layers of the corium carrying considerable amounts of melanin. There is a slight increase of pigment in the basal layers of the epidermis.

Treatment.—(1) 15–30% monobenzyl ether of hydroquinone in emulsifying ointment for one year, but little or no benefit, unless the pale areas interspersed in the pigment are due to the drug. (2) Ardena sun screen.

Comment.—This patient shows a slightly unusual picture on the face of a diffuse and follicular pigmentation, present for two years. About a year ago white areas appeared in the pigmentation and have remained very much the same. The pigmentation is quite unchanged except for the white areas since I first saw her.

I have no idea of the ætiology and I do not know what one would call this apart from melanosis. There is no mercury or silver in the section. We have not done patch tests with the cosmetics; she has continued to use the same cosmetics for the last two years.

POSTSCRIPT (January 1957).—Patch tests with cosmetics with and without exposure to sunlight were negative at forty-eight hours and there was no pigmentation after fourteen days.

Dr. I. B. Sneddon: I do not think Dr. Williams has excluded the possibility of cosmetics; I would have stopped her using cosmetic creams for a year. She can continue to use powder but I think it is the scent in the creams which causes this and it will take a year to fade.

Dr. C. D. Calnan: This case is similar to one shown to me by Dr. P. D. Samman at St. John's Hospital. When patch-tested she gave an eczematous patch to the face cream but only produced melanosis on the face.

Dr. H. Haber: I think the condition will stay a long time no matter what you do. The pigment lies within chromatophores and I cannot see how it can be removed by external remedies. It will take, I think, two to three years before any appreciable change will take place.

Dr. I. Martin-Scott: I think it is important that she should avoid *all* contact with scent. In a case of mine with deeper pigmentation involving the lower face and anterior aspect of the neck, the deep brown colour disappeared in eighteen months, when the woman ceased to use scented soap, powder and creams.

Dr. J. R. Simpson: Is 15% to 30% of the monobenzyl ether of hydroquinone used usually? I have found even 2·5% will produce a dermatitis.

Dr. H. Wilson: The worst case I have ever seen was a woman who demonstrated beauty creams; her face became so bad that the firm no longer employed her. The rash gradually got better after she changed her job, but I think it took two years.

Dr. F. Ray Bettley: Perhaps I could mention a woman whom I had in my ward because of this condition. She was using a well-known face-cream of a pinkish colour, containing eosin and some sort of safranine. When a patch test was done it gave negative results but it showed a sensitivity to ultra-violet light. I did the same patch test on the remaining 9 patients in the ward, and 8 out of 10 showed that this cream had the effect of producing a temporary light sensitivity in the test area.

Dr. Williams: I do not think this is the cosmetic type of pigmentation; the colour and the marked follicular reaction make me feel that it is different. I shall do patch tests, and shall tell her not to use make-up.

Tuberculoid Leprosy.—E. N. M. JOHNSTON, M.B., M.R.C.P. (for H. J. WALLACE, M.D., F.R.C.P.)

D. B., male, aged 20. Student. Siamese.

History.—In November 1955 this patient noticed numbness and an eruption involving the skin of the outer side of the right ankle. He was seen by Dr. G. Hodgson, who found an anæsthetic granulomatous lesion associated with thickening of the right lateral popliteal nerve. A biopsy showed a chronic inflammatory reaction in the dermis, mainly localized around the vessels and skin appendages, composed of lymphocytes and vacuolated reticulum cells. No acid-fast bacilli were seen.

Lepromin test strongly positive. *Chest X-ray*—no evidence of lung lesion.

Treatment.—A course of dapsone was started in April this year. The dose has been gradually increased to 700 mg. weekly. There has been steady improvement. A roughly triangular area of slightly scaling hypopigmented skin with peripheral superficial dilated vessels remains.

Dimorphous Leprosy.—E. N. M. JOHNSTON, M.B., M.R.C.P. (for H. J. WALLACE, M.D., F.R.C.P.).

N. H., male, aged 15. Anglo-Indian.

History.—This boy has been in this country for three years. He previously resided in Madras. Three months ago he noticed a non-irritating rash on his legs with numbness of the right thigh. The rash has since spread to the arms, face and trunk. Nasal discharge has been present for ten years.

Examination.—Skin: A symmetrical eruption of bluish-red oval macules and plaques of various sizes are present on the above sites. The edges of many lesions are ill-defined. Patches of hypopigmentation with anæsthesia are present in some of the above macules, but not all lesions are anæsthetic. *Peripheral nerves:* No significant enlargement. *Chest X-ray:* The lung fields appear clear. *Skin smear:* Positive for acid-fast bacilli resembling *M. lepræ*. *Nasal scraping:* No acid-fast bacilli. *Histology:* Changes of lepromatous leprosy with many acid-fast bacilli are present. *Lepromin test* negative.

Dr. W. H. Jopling: I would like to thank Dr. Wallace for asking me to say a few words about these patients. The first has a single lesion on one ankle which shows definite sensory loss, and, in addition, the common peroneal nerve is thickened. Such findings are pathognomonic of tuberculoid leprosy. The fact that no acid-fast bacilli can be demonstrated is of no importance for the diagnosis is made from clinical and histological evidence together with a strongly positive lepromin reaction.

The second patient is more difficult to classify. At first sight one might diagnose lepromatous leprosy but I would place him in the borderline (dimorphous) group as some of the lesions are atypical in appearance and have sensory loss. His positive skin smears, negative nasal scraping and negative lepromin reaction are all in keeping with borderline leprosy. These patients have an unstable immunity and if untreated they tend to progress to the lepromatous type. A few remain borderline or develop features of the tuberculoid type. My impression is that this patient will progress to the lepromatous type and it is therefore important to commence treatment soon.

With sulphone therapy the first patient will be cured within a matter of eighteen months but the second patient will require at least three years of treatment before skin smears become free from bacilli and it will be necessary to continue on a maintenance dose after that for at least five years, if not for life. This patient's dosage of sulphone must be increased cautiously in the early stages for treatment in borderline leprosy is liable to precipitate a type of "reaction" characterized by swelling and redness of the lesions associated with rapidly developing neural damage.

Atrophie Blanche.—R. H. MARTEN, B.M., M.R.C.P. (for SYDNEY THOMSON, M.D., F.R.C.P.).

J. L., male, aged 70. Retired.

History.—He has suffered from chilblains on the hands, feet and ears every winter since childhood. In recent years they have tended to break down and ulcerate but have caused him little or no pain. For the past five to six years he has noticed marked Raynaud phenomena and last winter he developed gangrene of the left little finger and left second toe. The patient thinks that some of the scarring on the hands and feet has occurred at the sites of ulcerated chilblains. He has never suffered from intermittent claudication or chest pain, although in recent years he has become breathless on exertion. He has never had any X-ray treatment.

Past history.—Red blotches on the palms as long as he can remember. Ten to eleven years ago an ulcer on the right heel treated by skin grafting. One year ago developed "blisters" on the left heel.

Family history.—Several members of his family have suffered from chilblains.

Examination.—On the backs of his fingers there are areas of atrophie blanche of varying sizes and shapes. In addition one or two of the lesions show small adherent keratoses. The skin over the terminal parts of the fingers is somewhat bound down but there is no true acrosclerosis. The palms of both hands are mottled and red and the left little finger shows loss of the distal two phalanges. On the dorsal aspects of the toes, feet and around the ankles there are similar patches of atrophie blanche. In addition, both feet show scattered dilated venules but no varicose veins; pitting œdema and some keratotic thickening over pressure points. Around the right ankle the skin is slightly pigmented while a small patch of dry gangrene is present on the left fourth toe. All the pulses in the lower limbs can be felt except the right dorsalis pedis which is absent. Blood pressure 210/110; no signs of heart failure. The nervous system is normal although the soles of both feet are hypersensitive to touch and sweating is more marked on the right side.

Investigations.—Hæmoglobin 98%; E.S.R. 25 mm. in the first hour (Wintrobe); blood urea 21 mg.%; blood W.R. negative; liver function tests normal; plasma proteins 6·45, albumin 4·65, globulin 1·8 grams %; no cryoglobulins found. Urine normal. Chest X-ray: Aortic arch is slightly wide but the heart shows no appreciable enlargement. X-ray of hands: No abnormality except deformity of the left little finger. No calcification or erosion seen.

Treatment.—Priscol 25 mg. three times a day to 50 mg. four times a day with some subjective improvement.

The following cases were also shown:

(1) **Lyrle's Disease.** (2) **Case for Diagnosis: Long-standing Dermatitis Clinically Like Pemphigus Foliaceous.**—Dr. D. I. WILLIAMS.

Syringocystadenoma.—Dr. R. H. MARTEN (for Dr. D. I. WILLIAMS).

Blue Nævus.—Dr. R. H. MARTEN (for Dr. SYDNEY THOMSON).

Mac o-ulcus Perstans (Castellani).—Dr. E. LIPMAN COHEN.

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Section of Neurology

President—D. W. C. NORTHFIELD, M.S., F.R.C.S.

[*November* 1, 1956]

MEETING AT THE NATIONAL HOSPITAL FOR NERVOUS DISEASES, QUEEN SQUARE, LONDON

THE following cases were shown:

Clivus Chordoma Presenting with Wasting of the Tongue.—Dr. F. E. DREIFUSS (for Dr. MICHAEL KREMER).

Ocular Myopathy.—Dr. ANTHONY COADY (for Dr. ERIC C. O. JEWESBURY).

Basal Arachnoiditis Following Tuberculous Meningitis.—Dr. C. J. EARL (for Dr. E. ARNOLD CARMICHAEL).

Abnormal Contraction in Triceps Muscles, Associated with Oleogranuloma Resulting from Penicillin Injections.—Mr. P. C. CAREY (for Mr. HARVEY JACKSON).

Colloid Cyst of the Third Ventricle Presenting with Dementia.—Mr. JOHN HANKINSON (for Dr. DENIS BRINTON and Mr. WYLIE MCKISSOCK).

Encephalopathy with "Myoclonus".—Dr. P. KYNASTON THOMAS (for Dr. MICHAEL KREMER).

(1) **Extensive Right Parietal Angioma with Cirsoid Aneurysm of the Scalp Associated with an Aneurysm of the Basilar Artery. (2) Left Frontal Angioma Together with Aneurysm on the Anterior Communicating Artery Successfully Treated at One Operation.**—Dr. L. J. HURWITZ (for Dr. MICHAEL KREMER).

Aqueduct Stenosis—Chronic Arachnoiditis.—Dr. G. F. SWANN (for Dr. J. HAMILTON PATERSON).

Hansen's Disease.—Dr. PETER EBELING (for Dr. J. PURDON MARTIN).

[*December* 6, 1956]

DISCUSSION ON THE EARLY MANAGEMENT OF SUBARACHNOID HÆMORRHAGE

Dr. J. MacDonald Holmes (Staffordshire General Infirmary and Midland Centre for Neurosurgery):

My contribution is to present the experience and conclusions of a general physician in a provincial non-teaching hospital concerning what I prefer to call spontaneous intracranial hæmorrhage, as subarachnoid hæmorrhage is commonly accompanied by intracerebral bleeding and the distinction between the two is an arbitrary one.

Spontaneous intracranial hæmorrhage is one of the most common and most rapidly lethal neurological emergencies encountered in the medical wards of a general hospital and it is generally acknowledged that the mortality in cases managed conservatively is in the region of 50%–60%. It is difficult to obtain accurate figures of the number of cases occurring annually in this country, but a reasonable estimate is probably between 4,000 and 5,000. At present only a small proportion of these are seen in the early and most dangerous stage of their illness by neurologists and neurosurgeons.

I am convinced that surgery in suitable cases is the only treatment which has much to offer in reducing the high mortality of conservative management, which is indicated in Table I, compiled from reviews in recent literature.

It would be impossible for neurosurgeons to assess, let alone treat, more than a small fraction of the cases which are admitted every day to the hospitals of this country. Ideally, all cases should be admitted to neurosurgical units, but it is improbable that this will be attainable on a nation-wide scale for some time to come. Surgery undertaken as an emergency measure for intracranial hæmorrhage necessarily carries a high mortality. This cannot fairly be compared with that of comparatively safe elective surgery undertaken during the phase of recovery, which has given rise to unduly encouraging mortality figures. This has led many people to say that conservative treatment is preferable at all stages of the illness, but I do not hold this view and would like to have the support of a neurosurgeon's opinion in all cases during the acute phase. This is not always available and it is therefore all the more

TABLE I.—MORTALITY RATES OF SUBARACHNOID HÆMORRHAGE AS GIVEN IN REVIEWS OF CASES TREATED CONSERVATIVELY

Authors	Date	No. of cases	Percentage initial mortality	Percentage survivors dying of recurrence
Taylor and Whitfield	1936	81	63	
Magee ..	1943	150	56	
Hamby ..	1948	130	52	22
Hyland ..	1950	191	53	21
Ask-Upmark and Ingvar	1950	138	28	23
Mount ..	1951	752	48	
Walton ..	1952	312	45	20
Wolfe ..	1953	93	56	
Present series		100	43	14

TABLE II. — INTERVAL BEFORE DEATH FROM LATE RECURRENCE IN THE PRESENT SERIES

8 of the 57 survivors of the initial illness died of recurrences during the fifteen-year period of follow-up. This gives a total mortality of 51% and a mortality from recurrences in the survivors of 14%.

Period in years	Number of cases
Less than one year	1
1–2	2
2–3	1, after a fourth recurrence
3–4	2, one after a third recurrence
4–5	1
11	1

important that general physicians, and particularly those in hospitals without a neurosurgical department, should have a knowledge of the essential methods of management and investigation of these cases, and be able to select those which are suitable for surgical treatment.

I have based my own views in the first place on a series of 100 consecutive cases seen during the fifteen years 1936–1951 and followed up during that period. I have excluded, perhaps wrongly, all cases of rapid or sudden death in elderly hypertensive or arteriosclerotic patients. The distinction between primary intracerebral hæmorrhage and subarachnoid hæmorrhage is clinically difficult and often artificial, but I was concerned more with the results of conservative management than the incidence of causes of bleeding.

By conservative management I mean rest in bed for at least one month, with good nursing care and all that it implies; attention to the bowels, bladder and skin, the prevention of dehydration, the judicious use of sedatives, antibiotics and sulphonamides, and cautious lumbar puncture to relieve headache.

This uniformity of management has not produced any remarkable lowering of the mortality in my cases during the initial stages of the illness, when compared with other published series shown in Table I, but the mortality from late recurrence is lower than that given in most reviews.

Tables II, III, IV, V and VI analyse briefly the data obtained from the 100 cases:

TABLE III.—DURATION OF FOLLOW-UP OF 57 SURVIVORS OF INITIAL HÆMORRHAGE

Period in years	Number of cases
1–2	15
2–3	10
3–4	5
4–5	5
5–6	7
6–7	3
7–8	2
11–12	1
13–14	5
14–15	4

TABLE IV.—INTERVAL BETWEEN ONSET OF HÆMORRHAGE AND DEATH IN CASES DYING IN HOSPITAL

Interval	Number of cases	Evidence of recurrence of bleeding
Less than 24 hours	14	0
Up to one week ..	8	4
1–2 weeks.. ..	15	12
2–6 weeks.. ..	6	6

TABLE V.—LESIONS FOUND AT NECROPSY IN 35 CASES

Anterior cerebral and anterior communicating aneurysms ..	10
Internal carotid aneurysms	2
Middle cerebral aneurysms	12
Posterior communicating aneurysms	4
Intracerebral hæmorrhage, no aneurysm found	4
Angiomatous malformations, one cerebellar, one parietal ..	2
Subacute bacterial endocarditis with multiple miliary aneurysms and intracerebral hæmorrhage..	1

In one case polycystic kidneys and a large aneurysm of the abdominal aorta were found. Six small aneurysms were found on the right middle cerebral artery.

In one case there were two aneurysms in the left middle cerebral distribution, one of which had ruptured.

Large intracerebral clots were found in 12 cases, but some clot formation was present in all the cases examined at necropsy.

TABLE VI.—FACTORS INFLUENCING THE PROGNOSIS IN 100 CASES TREATED CONSERVATIVELY

	43 fatal cases	57 survivors
Arterial hypertension (B.P. over 160 mm. systolic) ..	16	11
Coma at onset	24	9
Recurrence of bleeding during period in hospital ..	22	4
Previous history suggesting subarachnoid hæmorrhage	2	0

20 of the survivors had permanent neurological disabilities and of these 2 died within a year of further hæmorrhage. 4 patients were completely disabled by hemiplegia. 3 patients were completely disabled by dementia. All the other survivors were able to work to some extent. 4 were dysphasic, 3 had a III nerve palsy, 2 had a VI nerve palsy, 2 had a visual field defect and 2 were epileptic.

Since 1951, I have collected a further consecutive series of 79 patients, but up to now few of these have been followed up, so I do not know how many have died of recurrent hæmorrhage after leaving hospital. Some of these patients have been treated conservatively as before, some have been treated with hypotensive drugs in addition, whether hypertension was present or not, and some have been treated by surgical measures. Angiography has been used as a diagnostic aid in 37, or nearly half of these cases, and is absolutely essential if surgical treatment is to be considered. There has been much controversy as to whether angiography should be done in the early stages of the illness because of the risk of aggravating arterial spasm, but I am not convinced that the risk is a great one. If the condition of the patient is desperate I prefer to perform angiography soon after admission to hospital if it seems that on general clinical grounds surgery will be possible.

Table VII gives a brief analysis of this later group of 79 cases.

TABLE VII

Total number of cases	79
Total deaths during period in hospital	25
Mortality for all cases	31·6%
Cases treated surgically	17, with 4 deaths
Surgical mortality	23·5%
Cases treated with hypotensive drugs	30, with 9 deaths
Mortality in group treated with hypotensive drugs	30%
Cases treated conservatively as before	32, with 12 deaths
Mortality in group treated conservatively ..	37·5%
Angiography performed	37
Angiography failed	2

I have classified my 100 cases into four broad groups.

Group 1 includes fatal cases in which there is a rapid development of mid-brain or medullary compression from massive intracranial hæmorrhage, causing death in less than twenty-four hours. Treatment of any kind is useless in this type of case, of which there were 14 in the group of 43 fatal cases.

Group 2 includes cases in which there is a slower development of brain-stem compression, with gradually increasing stupor and neurological signs. In this group death occurs in from two to three days up to a fortnight after the onset, and there may or may not be clear-cut evidence of recurrent hæmorrhage. This type of case is the most important in which to consider surgical treatment and I think all should be investigated by angiography with the minimum of delay. There were 23 cases of this type in the 43 fatal cases. Also included in this group are those cases in which the symptoms simulate those of a cerebral tumour or abscess rather than hæmorrhage; there is no very abrupt onset and the changes in the cerebrospinal fluid may be equivocal and may not at first suggest that bleeding has taken place. There were three examples of this "pseudotumour" syndrome in the series.

Group 3 includes cases in which there is an interval of recovery from the initial hæmorrhage, followed by a fatal recurrence during the period in hospital. This happened in 6 cases of the 43 and it is probable that surgery undertaken in the quiescent period would save some of these cases.

Group 4 includes cases of undoubted hæmorrhage without loss of consciousness or only transient loss at the onset, progressing to complete recovery, or left with some neurological disability. There were only 8 deaths from late recurrent bleeding in the 57 survivors in this group and I think that surgery need not be considered when some months have elapsed since the acute stage.

It is in Groups 3 and 4 that decision between surgery and conservative management is most difficult. Generalization is impossible and the decision must be made on the individual case after careful assessment in consultation with the surgeon, and this must include bilateral carotid angiography with carotid compression on the side of the lesion, when one is found,

to determine the adequacy of the collateral circulation through the circle of Willis. When bleeding does recur at an early stage there is no doubt that surgery should be undertaken whenever possible.

To summarize, surgery should be considered at an early stage in the management of spontaneous intracranial hæmorrhage with the exception of patients who are moribund when admitted to hospital, or whose general physical condition or age makes them unfit for operation. The need for surgery will be the most urgent in those cases I have included in Group 2, with gradually increasing intracranial pressure due to large intracerebral clots or early recurrence of bleeding. The need for surgery is less insistent in those who are recovering, but again becomes urgent if bleeding recurs. My personal experience has not so far enabled me to decide whether elective surgery in recovered cases is of greater value than conservative treatment.

I would like to mention very briefly one case, clearly falling into Group 2, in which an emergency operation certainly saved the patient's life, and considering the site and nature of the lesion, produced a result which was satisfying beyond all expectations.

The patient was a woman aged 38, a physiotherapist, whom I saw on 8.12.55. She had had two very slight attacks of subarachnoid bleeding during the previous five weeks and five days before had a further severe hæmorrhage with the development of an almost complete left hemiplegia. She was semi-stuporous with occasional Cheyne-Stokes respiration. Bilateral papilloedema was present. She was transferred to the Midland Centre for Neurosurgery and a right carotid angiogram showed a loculated middle cerebral aneurysm arising from the region of the first branch of the right middle cerebral artery. Displacement of the vessels suggested the presence of a large intratemporal hæmatoma. An exploratory craniotomy was done the same evening by Mr. R. C. Connolly, who aspirated 80–100 c.c. of clot from the right temporal lobe. The aneurysm was seen to arise from the main stem of the middle cerebral artery and was so extremely thin-walled, that it was excised together with the portion of middle cerebral artery from which it arose. After a stormy convalescence this patient made an extremely good recovery, with hardly any trace of left hemiplegia. Her only disability is a left homonymous hemianopia, but this has not prevented her from being appointed as a director of physiotherapy. Post-operative angiograms show that the right middle cerebral artery is completely interrupted shortly above its origin.

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Dr. R. A. Henson (Neurological Department of The London Hospital and Maida Vale Hospital for Nervous Diseases):

Subarachnoid bleeding is a frequent concomitant of apoplexy, either as a result of extension of intraventricular hæmorrhage, or, more rarely, from direct rupture into the subarachnoid space. Such cases of primary cerebral hæmorrhage have been excluded from consideration in this communication. This is in some ways illogical as I have included a number of cases of cerebral angioma and tumour in my series, and in a few of these the hæmorrhage was primarily intracerebral or intraventricular: however, it is clearly necessary to include vascular hamartomas in the discussion, while the clinical picture in the tumours was apparently that of subarachnoid hæmorrhage, and this must explain my inconsistency. Secondly, this is not a discussion on the treatment of cerebral aneurysms and angiomas: the cause of bleeding is unknown in about one-half of my cases.

The diagnosis of subarachnoid hæmorrhage rarely causes difficulty: it is less easy to be certain that the bleeding is not originally intraventricular in some patients. The collection of the cerebrospinal fluid specimens in three separate tubes is a useful routine for the exclusion of the traumatic tap. It is sometimes difficult to decide just when the hæmorrhage has occurred and how many bleeds there have been in any one patient. Complaints of headache are often made over a period of some days before the obvious hæmorrhage occurs, and these episodes may indicate minor degrees of bleeding. Similarly there may be difficulty in diagnosing recurrences when the patient is in hospital, particularly in the comatose patient. In my experience minor degrees of hæmorrhage are uncommon in patients with demonstrable aneurysms. Small bleeds may be due to cerebral angioma, neoplasm or even blood dyscrasia, but more frequently they occur in patients in whom investigation reveals no cause for the bleeding. Small repeated bleeds are again rather characteristic of angiomas, and they also complicate the course of various neoplasms. Croft and I have recently drawn attention to the need for recognizing those patients in whom the subarachnoid hæmorrhage is spinal in

origin (Henson and Croft, 1956). The onset with sudden pain in the back is easily discerned, providing that early intracranial extension has not provoked cerebral disturbances, including impairment or loss of consciousness.

Table I shows the causes of subarachnoid hæmorrhage in an unselected series of 137

TABLE I

The London Hospital series—100 cases		Whipps Cross series—137 cases	
Cause known	55	Cause known 65 (47%)	
Aneurysms ..	34	Aneurysms ..	48
Mycotic aneurysm	1	Mycotic aneurysm	1
Cerebral angiomas	15	Cerebral angioma	1
Spinal angiomas ..	2	Spinal angioma ..	1
Blood diseases ..	1	Arteriosclerotic aneurysms ..	2
Neoplasms ..	2	Blood diseases ..	2
		Neoplasms ..	4
		Other causes ..	6

TABLE II.—AGE SCATTER OF PATIENTS WITH ANEURYSMS AND ANGIOMAS
(Age at Onset of Subarachnoid Hæmorrhage)

	Aneurysms		The London Hospital cerebral angiomas
	Whipps Cross	The London Hospital	
0–9	0	0	1
10–19	1	2	5
20–29	3	4	4
30–39	1	5	2
40–49	12	10	2
50–59	16	9	0
60–69	9	3	1
70–79	6	1	0
80–89	0	0	0
Totals	48	34	15

patients seen at Whipps Cross Hospital, and in 100 selected patients admitted to The London Hospital under the care of Sir Russell Brain or myself. There is no doubt that congenital cerebral aneurysm is the commonest cause. The diagnosis of aneurysm has to be made on probabilities as a rule; characteristic localizing signs are comparatively rare in an unselected group. Age is no barrier to the diagnosis. Post-mortem studies were done on 13 patients dying over the age of 70, at Whipps Cross Hospital, and in 8 of these the cause was a congenital aneurysm. Table II shows the age scatter at the time of the first hæmorrhage in patients with proven angiomas or aneurysms. There were 46 patients with hypertension, the diastolic pressure being 100 mm. of Hg or more, in the unselected series, and 26 died. Post-mortem examinations were carried out in 22 of these cases and revealed congenital aneurysms in 16. The disparity in the number of angiomas in the two series is probably accounted for by case selection and different age scatter. In the series of 15 angiomas seen at The London Hospital the clinical picture was sufficiently clear to allow of pre-angiographic diagnosis in all save one. There were 4 examples of spinal subarachnoid hæmorrhage in The London group and 1 in the Whipps Cross series, a total of 5 in 219 cases.

Diagnosis includes both discovery of the cause of bleeding and evaluation of the factors operating in the production of symptoms in an individual case. These factors include subarachnoid, intracerebral and intraventricular hæmorrhage, intracranial hypertension and its sequelæ, subdural hæmatoma and vascular spasm. The role of the blood pressure may also be important, whilst the development of atheroma in or adjacent to an aneurysm plays a part in determining the time of the bleed. The assessment of these factors in any one case may be virtuallv impossible, frequently several will be acting. In the moderate case of subarachnoid hæmorrhage with a brief period of altered consciousness and no focal signs, it is generally safe to assume that the important factors are the blood in the subarachnoid space and some degree of intracranial hypertension. Even in more severe cases, where the patient is comatose, recovery may occasionally take place without symptoms of cerebral damage, and here these same two factors plus vascular spasm may form the pathological mechanisms. In the comatose patient, however, intracerebral bleeding, usually with intraventricular extension, is the common finding. The importance of the intracerebral clot alone in the course of the disease does not appear to be great from my material. In all save 1 of the 15 cases of the series studied *post mortem* at The London Hospital the intracerebral hæmorrhage was associated with intraventricular bleeding. Subdural hæmatomata are not infrequently found at necropsy, usually with associated intraventricular and cerebral bleeding; no such lesions have been demonstrated by angiography in our cases. Vascular spasm is undoubtedly important. I had one patient who died with extensive cerebral infarcts which were presumably due to this mechanism. The differentiation of the focal disturbances due to intracerebral hæmorrhage from those of vascular spasm may be impossible both clinically and by angiography. Brain-stem hæmorrhages secondary to hypertension may cause death, the intracranial hypertension being produced by intracranial hæmorrhage or by the aneurysm itself acting as a space-occupying lesion. To summarize, the important factors are the hæmorrhage itself, subarachnoid, intracerebral and intraventricular, vascular spasm and intracranial hypertension. In severe cases all these mechanisms are usually operating.

Attempts to treat such patients by ventricular puncture, evacuation of intracerebral clot or decompression have been undertaken in only a few cases, for my surgical colleagues have not been anxious to interfere. When these methods have been used the results have been unhappy except in one patient whose intracerebral clot was evacuated with apparent benefit.

The difficulty of assessing the results of treatment of subarachnoid hæmorrhage is notorious. The mortality in patients treated medically appears to be in the region of 50%. I have not been able to discover a series of cases which have been offered the benefits of neurosurgical treatment which can be fairly compared with an unselected series treated medically. Patients admitted to neurological or neurosurgical departments have frequently survived the dangers of the first few hours or days; they are among the younger sufferers and serious concomitant disease is more commonly absent than in an unselected group. Neurological and neurosurgical series contain a relatively large number of patients with angiomas. My own material reflects these difficulties. I have a consecutive series of 137 patients admitted to Whipps Cross Hospital between the years 1950 and 1956. This series is unselected. The patients were persons whose affairs determined that they were in the region of the hospital when they were stricken; they were nearly all admitted at an early stage of the illness, many within hours and the vast majority within two days. On the other hand I have the series of 100 consecutive patients who were under the care of Sir Russell Brain and myself at The London Hospital between 1948 and 1956. This is a highly selected group. 43 patients were admitted as emergencies from the surrounding area or the neurological clinics, 12 were seen in private practice, but 45 were transferred from other hospitals. This source has latterly dried up as patients are usually referred to neurosurgeons. Generally speaking, patients were admitted much later in the course of the illness. 18 cases are common to both series. I have seen about 130 of the 219 cases in the acute stage. The two groups are in no way comparable. The age scatter shows a remarkable dissimilarity (Tables III and IV). The figures for The London cases are in line with those quoted by physicians from teaching hospitals. The Whipps Cross age scatter is more in accordance with that recorded by previous reporters of large unselected series. 35% were over 60. There is also a marked difference in the mortality, 27% in The London series and 49% for the Whipps Cross group: and yet 52 of the patients admitted to Whipps Cross were transferred to The London or Maida Vale Hospitals for investigation and possible neurosurgical treatment. This high mortality is accounted for by the number of cases admitted in a moribund state. 18 died within twenty-four hours, 35 within a week, and 45 within a fortnight of onset of bleeding. There was only one cerebral angioma in the series. Many of The London cases were admitted after the early period of danger was past, and there was a comparatively large number of angiomas.

In my unselected group of patients a clear policy of management has been gradually evolved, and it is of this series that I wish to speak. The follow-up is 100% to two months after the hæmorrhage and 87% to date. It was my original intention that surgical treatment should be provided for all patients who might conceivably benefit from it. Here I would like to thank my colleagues who have co-operated with me. Originally some heroic measures were adopted. Several seriously ill younger patients were transferred within a matter of one to two days: we gave up this policy for the simple reason that they all died, usually before angiography could be carried out. On the other hand we soon recognized, as have most other workers, that the danger period of recurrences in patients with aneurysms is maximal from the fifth or sixth to the fourteenth day, so recently we have aimed to transfer patients about the end of the first week, provided that age, associated disease and general condition do not contra-indicate this measure. We soon came to feel that if the patient could not weather the storm of the first bleed there was little to be gained by transfer. 52 patients were actually transferred. Table V shows the reasons for retaining the remaining patients and treating them medically. There were 85 in this group, of whom 49 died (58%). The mortality in the patients transferred was 37%. The difference is purely a reflection of the general condition of the patients and severity of the bleeding in the medically treated group. It does not seem to be the result of treatment by surgery. Many patients were clearly unsuitable for neurosurgical treatment on the score of age. About a quarter died in the first bleed, and one-half of these within twenty-four hours. The middle-aged and elderly patients frequently had serious associated disorders, obesity, severe hypertension, coronary disease, carcinomata, serious pulmonary affections; in fact the whole gamut of internal disease is covered in this group. Post-mortem examinations on patients who died do not suggest there were any major errors in judgment. There were 9 patients who were theoretically suitable for investigation but who were not transferred. Two refused, the other 7 were not seen by me, and it is rather ironical that all these 9 survived the initial bleed and were well at least two months later. 44 patients out of 52 transferred had angiograms. The missing 8 either died too soon or I changed my mind about the right course of management at a later stage in the illness. Table VI shows the results of angiography in both series. 14 of the 16 patients with negative angiograms survived; 1 died from carcinomatosis, which was

TABLE III.—137 PATIENTS WITH SUBARACHNOID HÆMORRHAGE
Whipps Cross Hospital 1950–1956 (deaths recorded in black)

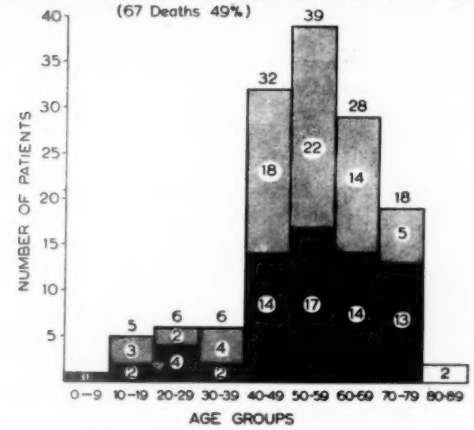


TABLE IV.—100 PATIENTS WITH SUBARACHNOID HÆMORRHAGE
Neurological Dept., The London Hospital, 1948–1956

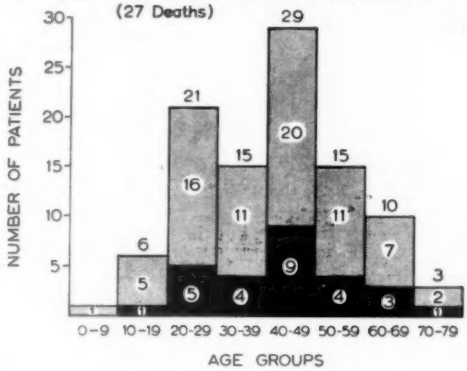


TABLE V

Whipps Cross series. Total 137 cases

Number transferred for investigation	52	Died	19	Survived	33
Reasons for non-transferral:					
Age alone (65 and over)	31	Died	19	Survived	12
Early death ..	17		17		—
Associated conditions alone ..	13	Died	5	Survived	8
Combined factors	15	„	8	„	7
No obvious reason ..	7	„	0	„	7
Patients refused	2	„	0	„	2
Total	85		49		36

TABLE VI.—RESULTS OF ANGIOGRAPHY

	Abnormal	Normal	Total
Whipps Cross series	28	16	44
London Hospital series	43	34	77

TABLE VII.—RESULTS OF SURGICAL TREATMENT

Aneurysms		Alive	Dead
Internal carotid—Posterior communicating—			
Carotid ligation ..	3	2	1
Direct attack	2	1	1
Anterior cerebral—Anterior communicating—			
Anterior cerebral clip	4	4	0
Direct attack	2	0	2
Anterior cerebral—Distal.			
Neck clipped	1	1	0
Carotid bifurcation—			
Carotid ligation	1	0	1
Direct attack	1	0	1
Totals	14	8	6
Cryptic hamartoma ..	1	1	0
Neoplasms	2	0	2
Totals	17	9	8

the cause of his hæmorrhage, the other had a further and fatal bleed, unfortunately there was no necropsy. Thus approximately one-third had negative angiograms and the consequent good prognosis which others have observed. Vertebral angiograms were only performed when specially indicated. In 1 patient angiography may have hastened death. 2 patients collapsed during angiography and the procedure was abandoned. Both recovered.

My surgical colleagues have co-operated closely in the treatment of these patients in the unselected group. They were invited to see the patients at an early stage and were sometimes warned of the impending arrival of cases of subarachnoid hæmorrhage. Table VII shows the various definitive surgical treatments carried out. The variety of these procedures, the differing times after hæmorrhage at which they were performed, and the small number of patients who came to surgery make it impossible to assess the value of any particular operation. The results of the operations in survivors are shown in Table VIII. Both patients

TABLE VIII.—ANALYSIS OF EIGHT SURVIVORS OF SURGICAL TREATMENT FOR ANEURYSM

	Complete recovery	Handicapped	Invalidism
Posterior communicating—internal carotid	2	—	1
Anterior cerebral—anterior communicating	3	—	1
Anterior cerebral distal	1	—	—
Totals	6		2

with internal carotid-posterior communicating aneurysms were left with partial III nerve palsies but were otherwise well on discharge. I have already commented on the results of measures to relieve intracranial hypertension or to evacuate intracerebral hæmatomata. The striking feature of these surgical figures is that they are so small. Out of 137 cases of subarachnoid hæmorrhage 52 were transferred for investigation; only 17 eventually underwent definitive operations for the causal lesion, and only 14 of these had aneurysms. This surely means that a vast amount of clinical material has to be combed to find a large series of surgically treatable aneurysms. I think it is also clear that in spite of a great deal of work by many people, the mortality from subarachnoid hæmorrhage in this particular series has only been slightly influenced for the better.

From this review of my own experience of an unselected series of patients with subarachnoid hæmorrhage I would suggest the following general lines of management. Firstly, the diagnosis must be established and an attempt made to define the cause on clinical evidence. There is probably little to be gained by transferring seriously ill patients as neurosurgical emergencies; they should be allowed to take their chance of weathering the first bleed. An exception should be made in those patients who develop symptoms of increasing intracranial hypertension without further bleeding, but these cases may be difficult to detect, and they are uncommon. If a patient survives his first bleed a decision must then be made whether to proceed to angiography, which would usually mean transfer to a special centre. The decision should be made within the first week so that the radiological examination may be carried out before the period of main danger of recurrence. In reaching this decision, age, general condition and the presence of associated illnesses should be considered. If there are symptoms or signs pointing to a diagnosis of aneurysm or angioma, angiography is called for unless other factors contra-indicate this course. Patients under the age of 40 should be investigated unless there are clear reasons for not doing so. With older patients each case should be decided on its own merits, and the decision should be made by a physician after a general appraisal of the case. Patients over the age of 55 are usually unsuitable for investigation with a view to surgery, but there are exceptions. A more conservative approach than this would be unwise until the value of hypothermia and advances in surgical technique have been evaluated.

Medical treatment consists of nursing care, maintenance of adequate airway, regulation of fluid balance, and the use of sedatives and analgesics. Meadows (1951) has discussed the important aspects of medical management. Hypothermia might prove helpful and is worthy of trial. Hypotensive drugs are probably best avoided, except in selected patients with established hypertension, and even then should be used with caution. It is my personal feeling that if we treat our next hundred unselected patients in conservative fashion, we shall show an immediate mortality and morbidity little higher than that of a comparable group in which all modern forms of diagnostic aid and surgical treatment are employed.

I wish to acknowledge the help of my colleagues, both clinicians and pathologists, in making their notes available to me.

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Mr. J. M. Small (Neurosurgeon—The Midland Centre for Neurosurgery and the United Birmingham Hospitals): The basis of my experience of intracranial hæmorrhage rests on some 158 cases which were admitted to hospital under my care. All these cases had a definite diagnosis of hæmorrhage and the series does not include apoplectic seizures in the elderly arteriosclerotic. Of these 158 with undoubted hæmorrhage 4 had some condition such as glioblastoma, secondary deposit or spinal lesion. The pattern of the disease in all these gave evidence that they were outside the usual groups. The 154 cases remaining fall roughly into four large groups (Table I). About half of these patients were treated surgically,

TABLE I

		Surgically treated			Surgical treatment not advised		
		Deaths	Clots		Deaths	Clots	
Aneurysms	46	11	} 10	41	14	} 5	
Multiple aneurysms ..	5	2		9	3		
Angioma	15	0	4	6	0	0	
No cause demonstrated	12	1	12	20	1	1	
Totals	78	14	26	76	18	6	

but the other half were refused surgical treatment for various reasons of age, arterial hypertension, multiplicity of aneurysms, the position and nature of the vascular anomaly, or because no cause could be found for the bleeding.

When we exclude the group which succumb in the first twenty-four hours, we are left with a group who are clearly dying—often with bilateral spasticity, deep unconsciousness and evidence of hypothalamic and vital centre failure. Angiography and tentative surgery are useless here. Others are in varying stages of drowsiness or unconsciousness with a variety of neurological signs.

The results of lumbar puncture are not always clear-cut and easy to interpret. The bleeding may be into the brain substance or the subarachnoid space and it may give that curious result of a polymorphonuclear or lymphocytic reaction in the cerebrospinal fluid. I have seen several patients who have had a diagnosis of brain abscess made under these conditions before coming for neurosurgical investigation. Rigidity of the neck and Kernig's sign may be absent and lead to confusion. This is true not only of those who are deeply unconscious.

As the hours go by the development of an intracranial compressive lesion becomes obvious. Although pupillary abnormality may occur at the outset the development of a dilating pupil is of great importance, declaring the onset of tentorial coning. In my cases 33% of those operated upon had intracranial clots and of these 26 patients 23 survive. Therefore, one of the important surgical principles is the evacuation of sizable clot with the treatment of the causative lesion at the same time.

With developing neurological signs and evidence of intracranial compression, angiography will be needed before surgical treatment can be undertaken. There may, however, be a marked spasm of the arteries in the vicinity of an aneurysmal hæmorrhage, which itself may be quite small, and this spasm leads to ischæmia and neurological signs, sometimes in the periphery of this blood supply and at a considerable distance from the source of the bleeding. It may also lead to areas of infarction and œdema. Angiography may suggest that a clot is present, but all that is found is a bulky area of brain due to œdema. Decompression may be of some use in such cases. There may also be structural changes in the walls of the arteries impeding blood flow, giving a beaded appearance on angiography. I would say that surgical treatment of an aneurysm at this stage is fraught with danger, and I can see no value in its application unless there is a sizable clot requiring treatment. The management of a patient in a period of cerebral ischæmia can undoubtedly be helped by hypothermia. Cooling by ice-packs reduces the oxygen requirements of the ischæmic areas of brain. In the seriously ill patient without a clot this treatment may carry him to a stage when full investigation and treatment may be undertaken.

This vascular spasm seems to last five or six days. We know there are relatively few deaths from recurrent bleeding in the first week, so that my view would be that elective angiography should be performed at about one week after hæmorrhage. Should this be applied universally to all cases of hæmorrhage? We will consider this later. My series contained only a few who had but one hæmorrhage and made a full recovery.

Of my 26 cases with compressive intracranial clots 2 have been subdural and the rest intracerebral. Only 2 have been in the frontal lobe, due to anterior cerebral aneurysms, the rest in the temporal or parietal area. Temporal lobe clots, usually arising from a middle cerebral aneurysmal hæmorrhage, are extremely dangerous because of the high incidence of tentorial coning. This may persist in spite of evacuation of the clot and treatment of the causative lesion, even when the intracranial pressure is low because the uncus becomes impacted between the tentorium and the mid-brain. Since experiencing this condition I have always divided the tentorium to release the uncal impaction. This is imperative, for

if the tentorial cone persists in spite of low intracranial pressure death is inevitable, and elevation of the temporal lobe in an attempt to free the uncus is not enough.

The clot can safely be removed as the bleeding point has always been in the wall of the clot cavity, and never centrally placed in the clot. The clot also seems to have some predilection for a certain position in the temporal lobe, in particular it forms in a paraventricular position running along the side of the temporal horn as though there were some cleavage plane in this position which decides the course of the blood extravasation. In nearly half of my cases no angiographic cause of the intracerebral clot was demonstrated, but at operation an aneurysm was sometimes found or a tiny angiomatous area existing in the cortex, and there is no doubt that these tiny angiomata can cause very considerable intracerebral bleeding.

Some patients become drowsy without advance in neurological signs or evidence of compression, and suffer some upset in their fluid and and crystalloid balance and a low blood pressure. I have attributed this condition to pituitary infarction, and it is not surprising that aneurysms in the parasellar region should bring these problems in their wake, and the use of ACTH or cortisone in this group of patients is of the greatest value.

I am still not sure whether elective angiographic investigation should be performed under general or local anæsthesia. I think that in skilled hands general anæsthesia is preferable, and guards the patient from upset in the examination. Percutaneous angiography should be performed first on the affected side and followed by an angiogram on the opposite side. The angiogram may fail to reveal a tiny aneurysm or one occluded by clot, nor does the absence of a demonstrable lesion prove that there is no danger of fatal hæmorrhage in the future.

To have a full arterial picture a vertebral angiogram should be performed as well but I do not use this investigation without specific indications. Although aneurysms occurring in the posterior fossa can have surgical importance, they have been only of post-mortem interest in this series.

In my series there have been no deaths in the 21 cases of angioma which form 14% of the entire group, either in the 15 operated upon, or in the 6 in whom no surgery was undertaken. Hæmorrhages for which no cause can be found angiographically, 20% of this series, have had an equally satisfactory result. The 12 patients operated upon were all for large intracerebral clots—11 survived; and in the 20 who bled—some of them on more than one occasion—in whom no surgery was necessary, all have survived but one.

For 200 years surgeons have been interested in the treatment of aneurysms, and the principles of treatment are clear: the Hunterian principle of proximal ligation; the exclusion of the aneurysmal sac by the method of Matas; and the total removal of the aneurysm and its feeding vessels. It is on the basis of these principles and their effectiveness applied to intracranial aneurysms that surgical treatment must be considered.

Proximal ligation of the carotid artery is certainly not indicated in the acute stage with the vascular spasm at its height. Its only value can lie in aneurysms directly related to the carotid artery and its bifurcation. In this series 18 patients have had carotid ligation for such an aneurysm—some of them the common carotid alone, others the internal, or both—with 1 death and 1 hemiplegia, but there have been 2 late recurrent fatal hæmorrhages from the carotid aneurysm after two or three years.

The aim should be to obliterate *the aneurysm and its neck* from the circulation. Some aneurysms lend themselves to opening and packing with muscle; whilst in certain positions of the circle of Willis, particularly the anterior cerebral, proximal occlusion of this artery would appear to be of considerable value as it forms a cul-de-sac with probable thrombosis including the artery and the aneurysm. Wrapping the artery over its outer surface with muscle or cotton has been followed by recurrences in my hands, and some of these have been within twelve hours of this procedure.

In patients who are making a satisfactory recovery without residual disability, and have had but one hæmorrhage, the likelihood of a recurrence is considerable; the anxiety of recurrence in the minds of many of these patients is enormous. Angiography at the end of the first week after hæmorrhage should be undertaken in the majority of these people to determine the position of the aneurysm, to give some prognosis and to decide whether surgical treatment is advisable. An aneurysm on the back of the carotid artery on the non-dominant side, or on the posterior communicating, can usually be treated simply, safely and soundly. One on the middle cerebral artery of the dominant hemisphere would be an entirely different problem in a perfectly well patient—a fear of dysphasia from surgical procedure should halt the surgeon's hand. So we might pursue the position of the varying vascular anomalies to decide their safety for surgery. We still do not have all the information we require to determine the necessity for treatment in varying positions, and this alone is sufficient justification for investigation of these patients.

The value of a dry field by temporary vascular occlusion in the cooled patient is already improving the surgery of direct attack, with a higher percentage of good results.

Section of Surgery

President—Eric A. Crook, M.A., M.Ch., F.R.C.S.

[*October* 3, 1956]

DISCUSSION ON THE MANAGEMENT OF THE GANGRENOUS FOOT

Professor C. G. Rob (St. Mary's Hospital, London):

Gangrene of the toes and feet may be due to arrest of the arterial or of the venous flow, the latter accounting for less than 1% of cases. I shall describe those methods of treatment which aim at restoring the circulation to a gangrenous limb, because it is surprising how minimal the tissue loss may be after a successful procedure carried out by these newer methods.

Cause.—In most patients the cause of the gangrene is atherosclerosis and Table I lists the causes of gangrene of the toes and feet in 145 patients who have been under the care of the Surgical Unit at St. Mary's Hospital since 1950.

TABLE I.—CAUSES OF GANGRENE OF THE LOWER LIMBS OF 145 PATIENTS (18 BILATERAL)

Atherosclerosis	125	
Main vessel occlusions		90
Small vessel occlusions		11
Main and small vessel occlusions		24
Thromboangiitis obliterans	12	
Embolus	6	
Infective gangrene in a diabetic	4	
Venous gangrene	3	
Arterial injury	3	
Dissecting aneurysm. Thrombosed aneurysm. Raynaud's phenomenon	2	each
Polyarteritis nodosa. Neonatal. Congenital arterio-venous fistula.		
Radiotherapy	1	each

Treatment.—This includes control of diabetes and infection, stopping patients smoking (at least those with Buerger's disease), maintenance of normal blood pressure and hæmoglobin level particularly in patients with an acute arterial occlusion, and the treatment of any other general disease. The management of the gangrenous foot itself may be conservative or operative, but it is important to stress that the plan of conservative management outlined here should be adopted routinely before and after operation in those patients who are treated surgically.

CONSERVATIVE MEASURES

Reduction of the metabolic needs of the part.
Relief of pain.
Development of the collateral circulation.
Anticoagulants.
Maintenance of the patient's general health particularly the hæmoglobin level.
Prevention of infection.
Prevention of deformity.

The limb should be placed at rest flat in bed and on no account elevated, but short periods of dependency may be permitted. It should be kept cool and the patient as a whole heated to produce reflex vasodilatation. Sleep should be encouraged by relief of pain; alcohol is effective in many patients for this and assists vasodilatation. All splints and dressings

should be loose. Lumbar sympathetic nerve block may help. Infection should be prevented with local and systemic antibiotics. Anticoagulants are of value in many patients, and in our view they need not be stopped for surgical procedures, should these become necessary, because, if heparin is used and hæmorrhage appears to be excessive, protamine sulphate works as an efficient antidote in a few minutes. We have not had trouble from hæmorrhage during operations when patients have been taking the other anticoagulants under proper control.

Surgical Treatment

Sympathectomy.
An arterial reconstruction operation.
Amputation.

Every patient with a gangrenous foot should have an arteriogram if his general health is satisfactory and if there is evidence that the cause of the gangrene is occlusion of a main artery. Evidence of occlusion can be obtained by feeling the arterial pulses in the limb; if the femoral pulse is absent then it is good news because the patient will have an aortic or iliac occlusion and an arterial reconstruction operation should be successful; a palpable femoral but absent popliteal pulse means that an arterial reconstruction operation is still a possibility, but the presence of either ankle pulse with gangrene rules out a large vessel occlusion. An arteriogram serves to localize the occlusion and enables the surgeon to plan his operation.

Arterial reconstruction.—This is the treatment of choice. It has changed our whole approach to the gangrenous limb and such statements as "when the gangrene has spread to the dorsum of the foot an above-knee amputation is necessary" now belong to surgical history. The artery may be reconstructed in a variety of ways but, in general, the best results follow thromboendarterectomy, if the vessel is large, or the by-pass homologous arterial transplant inserted in the manner recommended by Cockett. Fig. 2 shows a good lesion for an arterial reconstruction; an occlusion of a large vessel with a reasonably satisfactory arterial lumen above and below the occlusion. Figs. 1 and 3 show the right foot of this patient, who was aged 52, before and six months after a successful thromboendarterectomy; only local tissue loss has occurred whilst without an arterial reconstruction procedure an above-knee amputation would have been necessary.



Fig. 1.—The foot of a dental surgeon aged 52. He has had a lumbar sympathectomy and an amputation of the great toe. The progress of his disease had not been arrested. Severe rest pain persisted.



Fig. 2.—The arteriogram from the patient shown in Fig. 1. He has a localized occlusion of the popliteal artery. An arterial reconstruction operation (thromboendarterectomy) was successful.

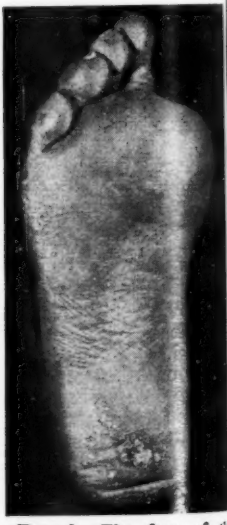


Fig. 3.—The foot of the patient shown in Figs. 1 and 2. He is back at work.

Table II shows that we have found it possible to perform an arterial reconstruction

TABLE II.—OPERATIONS FOR GANGRENE OF THE LOWER LIMB—145 PATIENTS (18 BILATERAL)

Arterial reconstruction	30		Amputation ..	94	
Successful		20	Level with healing		
Unsuccessful		8	Above knee ..		34
Dead		2	Below knee.. ..		26
Embolectomy ..	3		Syme		2
Sympathectomy ..	81		Transmetatarsal ..		7
Of value		55	Toe or toes.. ..		19
Valueless		24	Local excision ..		4
Died in hospital ..		2	Died in hospital ..		2
			Nothing surgical	12	
			Died in hospital ..		2

operation on 30 or 20·6% of our patients with gangrene seen during the last five years and that 20 of these have been successful. A review of the patients included in Table II makes it apparent that, with the knowledge we have to-day, a greater number of these limbs could be saved. In our view about 25% of patients with gangrene of the toes or feet due to arterial disease can have their limb saved by an arterial reconstruction operation. This will mean a large number of unnecessary arteriograms but the number of limbs saved will justify the trouble.

The *selection of patients* with gangrene for arterial reconstruction depends to a greater extent upon the state of the arteries as shown on the arteriogram than upon any other factor. Because the alternative is a major amputation one need not be deterred by coronary artery disease or evidence of advanced generalized atherosclerosis. If the patient is fit enough for a major amputation he is fit enough for an arterial reconstruction operation. The essential feature on the arteriogram is an adequate artery distal to the occlusion; not only is the size of the vessel important but also the state of the vessel wall. While the best results will follow in patients with aortic or iliac occlusions, in exceptional circumstances a good flow may be re-established when the occlusion has spread as far down the limb as the bifurcation of the popliteal artery. A patient aged 36 had thromboangiitis obliterans; he had previously lost his other leg below the knee but had not stopped smoking, and he had advanced gangrene of his only foot and ankle and an above-knee amputation appeared to be needed. At operation a by-pass autogenous vein graft was inserted from the lower femoral artery to the posterior tibial artery which has worked well. In such a patient little harm is done even by an unsuccessful operation because the arterial reconstruction procedure is performed on that part of the patient which would otherwise have been amputated.

Type of arterial reconstruction operation.—In patients with gangrene the best procedure is a thromboendarterectomy (9 of our 30 patients had this type of operation). This is because a mild wound infection is by no means uncommon when there is an infected gangrenous lesion of the foot, and such infection causes little trouble when no foreign material has been inserted but may cause secondary hæmorrhage from, or thrombosis of, a homologous arterial transplant. When it is not possible to perform a thromboendarterectomy, a by-pass procedure using either a homologous arterial transplant or an autogenous vein graft gives good results, but we have to date found plastic prostheses unsatisfactory if one end has to pass below the inguinal ligament, although we find these materials satisfactory for the reconstruction of the aorta or iliac arteries.

Post-operative management.—Firstly, long-term anticoagulants should be given to every patient who has had an arterial reconstruction operation for thrombosis of an atheromatous artery. He should take them, if possible, for the remainder of his life. This is of particular importance in patients who had gangrene. We use phenylindanedione (Dindevan) for this purpose and consider that we may by this means reduce the incidence of recurrent thrombosis in the reconstructed arterial segment and of fresh thromboses in other arteries.

Secondly, the management of the apparently gangrenous parts: if the arterial reconstruction procedure restores palpable pulsation in the arterial tree distal to the occlusion, then at least six weeks should be allowed to pass before any form of amputation is undertaken. With a conservative approach of this kind it is surprising how apparently gangrenous tissues can recover with the line of demarcation forming well distal to where it was originally expected to be. The reason for this is that gangrene of the skin extends farther in the superficial than the deep layers; therefore after an efficient arterial reconstruction operation the deeper layers recover and when the dead superficial layers have peeled off a sound layer of

skin will be present underneath. The foot often remains swollen and œdematous for some months and an elastic bandage should be worn during this time.

Sympathectomy.—This is a most useful procedure, but it is important that the level of ganglionectomy should be such that the collateral circulation around an arterial block and the skin at the level of an amputation should be denervated. The skin of the lower limb is deprived of its sympathetic nerve supply as far as the supracondylar level of the femur by removal of the 2nd and 3rd lumbar ganglia. Inclusion of the first lumbar ganglion raises the level of skin denervation to the groin and if the whole buttock area is to be denervated the ganglionectomy should extend to the level of at least the 10th dorsal ganglion.

This means that a ganglionectomy designed to assist the healing of a mid-thigh amputation must include the 1st lumbar ganglion. If the lower ganglia only are removed the area of skin denervation will be entirely within the amputated portion of the patient. Similarly, if the arterial occlusion is in the lower aorta or iliac arteries the ganglionectomy should be from the 3rd lumbar to the 10th dorsal level at least, so that the lumbar and gluteal collaterals around the occlusion will be denervated.

Amputations.—We believe that conservative amputations should be used as often as possible; first the toes, next transmetatarsal, very occasionally a Syme, sometimes below-knee, occasionally Stokes-Gritti, and then the above-knee or mid-thigh amputation. In addition, in diabetic patients with infective gangrene a purely local operation removing all dead tissue but following no set plan is the treatment of choice. On 4 occasions in diabetics we have obtained primary healing after removal of one or more toes, the corresponding metatarsals and adjacent soft parts.

The transmetatarsal is a particularly valuable operation when the circulation is good enough for primary healing to take place. As will be seen, we have used this procedure on 7 occasions. This operation has the great advantage that an artificial limb is not needed. The Syme amputation is only occasionally satisfactory in patients with arterial disease; our 2 patients had palpable ankle pulses but gangrene of the dorsum of the foot where the flaps of a transmetatarsal amputation would have been placed and the Syme amputation healed well. The below-knee amputation is probably the most difficult, requiring a meticulous technique and two-layer closure if primary healing is to occur. We have had little experience of the Stokes-Gritti procedure which is favoured by some. The above-knee amputation has the advantage that healing is certain.

Venous gangrene.—This is a rare lesion. We have seen 3 cases in the last five years. One was in a girl of 13 who had ulcerative colitis and both the others were in patients with advanced intra-abdominal cancer. The cause is thrombophlebitis of the ileofemoral vein and the gangrene is due to thrombosis of the small vessels in the area of the gangrene, or to severe arteriolar spasm. Treatment is by elevation and anticoagulants, amputation being delayed until it becomes inevitable.

SUMMARY

(1) The treatment of choice of a gangrenous limb is to restore the circulation with an arterial reconstruction operation. This was carried out successfully in 20 or 13·7% of our 145 patients with gangrenous toes and feet and the tissue loss was small.

(2) When this is not possible sympathectomy may help but an amputation is often necessary. The level of sympathetic denervation should be planned to fit each individual patient.

(3) Amputations. The transmetatarsal gives very good results when the circulation is sufficient for healing. In diabetic patients with infective gangrene a purely local excision of dead tissue will suffice.

(4) After an arterial reconstruction operation for a lesion of this type the patient should take anticoagulants for the rest of his life.

ACKNOWLEDGMENTS

I wish to thank Mr. H. H. G. Eastcott and Mr. Kenneth Owen who performed many of the operations referred to in this paper and the other members of the Surgical Unit at St. Mary's Hospital for their help with the management of these patients.

Dr. Wilfrid Oakley (King's College Hospital, London) first discussed the relationship between diabetes and peripheral arterial disease, and brought forward figures in support of the argument that the latter was more closely related to old age than to the duration or severity of the diabetes. The high incidence of foot lesions in the diabetic could in large measure be accounted for by the coincidence of neuropathy, arteriosclerosis and sepsis.

The frequency of purely neuropathic conditions affecting the lower limbs, and especially the feet, in diabetics had not in the past been appreciated, and a number of slides showing

typical examples of perforating ulcers, localized gangrene, Charcot joints and a characteristic dorsal dislocation of the toes was shown.

Lesions of the feet in diabetes could be subdivided into four types: Septic, neuropathic, ischæmic and combinations of these three. Septic lesions should be treated in the same way in the diabetic as in the non-diabetic; neuropathic lesions responded well to local surgery while ischæmic lesions or those complicated by this factor often required more radical surgery. In such cases local surgery only succeeded when skin cover could be obtained without tension, and it was unwise to close the wound with sutures. When amputation was necessary it should be carried out below the knee by the Silbert technique.

Lastly, Dr. Oakley (Oakley *et al.*, 1956) described a method for protecting the heels in cases with ischæmia of the feet; this consisted of suspending the lower limbs in canvas slings by means of long springs connected to a beam above the bed. Since the introduction of this device, no trouble had been encountered with ulceration or gangrene of the heels in diabetic patients at King's College Hospital.

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Mr. G. E. Mavor (Royal Infirmary, Aberdeen):

I wish to concentrate on atherosclerosis, particularly as it affects the arteries distal to the inguinal ligament. Firstly, I would like to take a step back from the picture of established gangrene, and consider the events which immediately precede it. Secondly, I shall consider the use of the by-pass arterial graft and mention some of the technical points involved.

It is now recognized that the onset and spread of secondary thrombosis in the arterial tree, particularly above the knee, follows a distinct pattern (Mavor, 1956*b*). Initially thrombosis is limited, the collateral circulation being adequate to meet the resting needs of the limb. However, the thrombus propagates in the main vessel and failure of the collateral circulation with involvement of the lower leg vessels by thrombosis results in gangrene.



FIG. 1.—Main vessel thrombosis which has been halted by the branches of the mid-portion of the popliteal artery. The distal segment of the popliteal artery is free of branches and healthy.

The failure of the collateral circulation is heralded by rest pain, the affected foot being discoloured, hyperæsthetic and cold. At this stage the main vessel is extensively thrombosed, the proximal limit of the thrombosis being the origin of the profunda femoris artery. This is the stage of femoro-popliteal thrombosis. In many of these patients, thrombus propagation distally may be temporarily halted by a cluster of small arteries about mid-popliteal level, the terminal inch or two of the popliteal artery remaining patent (Fig. 1). This segment of vessel is below knee-joint level, free of branches, usually healthy and easily accessible. Its existence makes the insertion of a shunt graft feasible even at this late stage in the development of peripheral ischæmia.

The lower leg vessels are rarely the site of initial thrombosis in atheroma and gangrene only results when the thrombosis is extensive in both anterior and posterior tibial, or in the case of digital gangrene, when the digital arteries are occluded. In the presence of main vessel thrombosis of limited extent, the lower leg vessels are often healthy and patent. As the collateral circulation fails, thrombosis occurs in the lower leg vessels, often in multilocular fashion, and further clinical deterioration is inevitable. The occurrence of secondary thrombosis in the lower leg vessels is an important event, because any arterial restoration procedure on the main vessel may be compromised.

The final stage is gangrene, resulting commonly from involvement of the lower leg vessels either by propagation of thrombus from the main vessel or, more commonly, by multilocular thrombosis within them (Table I). Extensive small vessel thrombosis and digital thrombosis are fairly uncommon. Peripheral arterial embolism and extensive degenerative disease with thrombosis together comprise about 25% of all cases. In the latter, there has been no

TABLE I.—PATHOGENESIS OF GANGRENE IN 43 CASES

Extensive main vessel thrombosis	26
Extensive degeneration and thrombosis ..	6
Extensive small vessel thrombosis	2
Digital thrombosis	4
Peripheral embolism	5

evidence of prior peripheral arterial insufficiency. Thrombosis, the result of atheroma, commences at more than one point in an extensively diseased arterial tree, and as there is no collateral circulation extends rapidly. The prognosis in this gangrene of the aged is bad and major amputation inevitable.

It is apparent that in approximately 60% of cases, gangrene is the culmination of many years of increasing peripheral arterial insufficiency caused by the slow extension of main vessel thrombosis and finally precipitated by involvement of the lower leg arteries. Although in certain cases even after gangrene results, the limb may yet be saved, as Professor Rob has shown, surgically the problem is more easily dealt with at some time prior to the onset of gangrene. However, once the stage of femoro-popliteal thrombosis has been reached, the time available for such surgery is limited, as most patients with rest pain and skin changes in the foot develop gangrene in 1 to 6 months.

THE USE OF SHUNT ARTERIAL HOMOGRAFTS

The shunt or by-pass arterial graft has certain technical advantages. Of great importance is the fact that the anastomosis can be kept at a workable size, as the graft obliquely cut or divided up one aspect can be jointed to any length of slot in the host artery even if the latter is small. Exact matching of graft and host artery is not necessary and the suture line is always the widest part. The prepared end of the graft is first sutured to the host artery by the insertion of an everting mattress suture at each end of the incision in the host artery, thereafter a continuous over-and-over suture is quite satisfactory, and during suturing the host artery wall is best penetrated from within out to avoid any possibility of pushing thickened or calcified intima off the media.

Among the advantages are the preservation of all collateral channels and the feasibility of locating the anastomoses, both proximal and distal, at the most suitable points.

Our experimental experience with over 70 cases using homologous artery, autogenous vein and crimped nylon as shunts in small arteries (Hinshaw *et al.*, 1956) indicates that from the point of view of both early and late thrombosis an arterial homograft is to be preferred. My clinical experience is limited to 22 cases. There are two groups of cases:

The first group consists of patients with occlusion of the superficial femoral artery. All these patients had calf claudication as their main complaint. None had rest pain, and except for one case, none had skin changes referable to the foot. Average age was 57 years, and average length of graft 13 in. Pre-operatively, no ankle pulses were palpated. In each case, except one, arteriography revealed a healthy proximal popliteal, and the distal anastomosis was fashioned here. In the remaining case, the proximal popliteal was considered markedly atheromatous, and the site for the distal anastomosis was the distal segment of popliteal artery.

In cases of femoral artery thrombosis, irrespective of the extent, the progression of secondary thrombosis is such that the proximal anastomosis should always be proximal to the profunda femoris origin. In this way the profunda femoris origin serves to protect the orifice of the graft from propagating thrombus. The distal anastomosis can be to either the proximal popliteal if this is healthy, or if it is not, to the distal segment of the popliteal artery. The latter may be the better choice in many cases as the distal orifice of the graft is protected by the numerous collaterals arising from the mid-part of the popliteal artery. In cases of popliteal artery thrombosis of limited extent which are amenable to a shunt graft, the proximal anastomosis may be better fashioned proximal to the profunda origin, although further experience in such cases is necessary.

In all cases post-operatively, the patient developed a warm comfortable foot and symptoms were completely relieved. In each instance, except for the case with skin changes, both anterior and posterior tibial pulses were palpated. The longest follow-up period is fourteen months. In one case, that with skin changes, already referred to, the graft thrombosed after five months. This occurred during the night and resulted in the immediate return of calf exercise pain next day. It is considered significant that this patient had small-vessel atheroma with thrombosis. The immediate post-operative hyperæmia, expected after grafting (Rob, 1953), was very limited, and no ankle pulses were noted.

The second group consists of cases with femoro-popliteal thrombosis. All these patients had calf exercise pain with an exercise tolerance of under 100 yards in each case, rest pain and ischæmic

changes in the foot, and two had gangrenous lesions. Average age was 64 years, and average length of graft 20 in. Post-operatively, symptoms were relieved in each case and the gangrenous areas healed. No post-operative ankle pulses were noted except in one case, in which the anterior tibial pulse was palpated.

In cases of femoro-popliteal thrombosis, the graft has to run from the main vessel just proximal to the profunda to the distal patent segment of the popliteal artery. The lower anastomosis should be fashioned first, and an intermediate incision is necessary in the thigh to help tunnelling and positioning of the graft (Figs. 2 and 3).



FIG. 2.



FIG. 3.

FIGS. 2 and 3.—Femoro-popliteal thrombosis, treated by insertion of a 20-in. shunt arterial homograft. Fig. 2 shows the extensive main vessel thrombosis, poor collateral circulation, and short patent distal segment of popliteal artery. Fig. 3 is the post-operative arteriogram, three months after operation.

The longest follow-up period is eleven months. In one instance the graft thrombosed after eight months. This occurred during a two-and-a-half-hour motor-car journey, the patient being a passenger in the back seat. During the journey she felt discomfort behind the knee, and at the end noted return of calf exercise pain. She has since had a lumbar sympathectomy, and her condition remains satisfactory, with no return of rest pain or gangrene.

Sympathectomy has been carried out in the other 4 patients in this group, and they are also on prolonged or permanent anticoagulant therapy, started about four weeks post-operatively.

The one instance of late thrombosis seems the result of prolonged flexion of the knee-joint. Such an experience confirms experimental findings, where constriction of a homograft at the groin in dogs is not uncommon (Mavor, 1956*a*). Patients with long grafts crossing the knee-joint should be warned against sitting with their knees flexed for prolonged periods.

In conclusion, the justification for a grafting procedure in cases of limited segmental thrombosis is uncertain, because the end-result of the operation is unknown. If the shunt graft will remain patent for ten to fifteen years, then the operation is justified. Objections

to the procedure lie partly in the fact that the diversion of blood through a large shunt will reduce the flow through the existent collateral channels, which may not enlarge or may even thrombose.

In cases of femoro-popliteal thrombosis, operation appears justified. The prognosis as regards gangrene in such cases is usually bad; sympathectomy will improve this, but only to a limited extent. Although it may relieve rest pain it will not uniformly benefit claudication, which by this time may be crippling. This, moreover, is the last opportunity to restore the main arterial trunk of the leg, and it should be taken. When gangrene has developed or is impending, cerebral, renal or cardiac manifestations of the disease are not always contra-indications to operation. Associated sympathectomy and permanent anticoagulant therapy may prolong the period of patency of the graft.

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Mr. E. C. B. Butler (London Hospital):

In the treatment of gangrene of the feet, apart from vascular surgery, the improvement in results has been mainly due to the control of sepsis by systemic chemotherapy. This is best demonstrated in the better results now obtained in patients suffering from diabetes. During the past six years we have treated 123 cases of gangrene of the feet:

Arteriosclerotic.. ..	51
Thromboangiitis ..	11
Diabetic..	58
Frostbite	1
Embolic..	2
	123

Arteriosclerotic.—Males 47, average age 65, females 4, average age 68.

In 48 of these patients either the popliteal pulse was absent or there was minimal pulsation with the oscillometer below the knee.

Above-knee amputation ..	45	Two died, aged 76 and 82 years.
Sympathectomy	1	Partial relief.
Below-knee amputation ..	1	
Formal amputation toe ..	1	

In our experience below-knee amputation for these cases was not a success; it was done in three patients as a primary operation but the wounds did not heal and a higher amputation was done.

In the three remaining patients of this group the popliteal pulses were palpable and a below-knee amputation was successful. The total mortality was 3·9%.

Thromboangiitis obliterans.—There were 11 males; average age 45.

Most of them had already had lumbar sympathectomy with temporary improvement.

Above-knee amputations were done in 9 cases, below-knee in 2. Healing was satisfactory and there were no deaths.

The majority of these patients rapidly become used to their artificial legs and lead quite active lives.

Diabetic.—For many years it has been realized that infected feet in diabetics fall into two classes.

One has all the signs and features of a spreading infective necrosis due to the blocking of a main vessel. The treatment of this group is the same as in those due to atherosclerosis except that infection is usually present.

The second group occurs in younger patients whose main arteries are patent, but who suffer from trophic disease of the feet with secondary perforating ulcers, osteomyelitis, or spreading necrosis of the tendons or fascia. A major amputation is rarely required as

the response to local surgery is good. The results obtained in both groups of diabetic necrosis have dramatically improved since the introduction of penicillin.

Without penicillin	38 cases		
Absent popliteal pulse	20		
Above-knee amputation		7	2 died
Local surgery		13	2 died
Positive popliteal pulse	18		
Above-knee amputation		1	died
Below-knee		4	2 died
Syme		3	
Amputation of metatarsals		2	1 died
Local excision		8	

6 of these deaths were due to anaerobic gas cellulitis which rapidly turned to spreading gangrene; death was due either to severe toxæmia or a terminal bacteriæmia. The organisms concerned were anaerobic streptococci with fusiform bacilli; *Cl. welchii* was never demonstrated. The total death rate was 20%.

During the past six years 58 cases have been treated.

Popliteal pulse absent 24. Males 8, average age 68; females 16, average age 70.

Treatment:

Above-knee amputation	23	3 died
Amputation toe ..	1	

Positive popliteal pulse 34. Males 11, average age 57; females 23, average age 63.

Treatment:

Above-knee amputation	1	died
Below-knee	8	
Syme	1	
Amp. of metatarsals ..	5	
Amp. of toe or toes ..	14	
Sympathectomy	1	
Excision of dead tissue with grafting	4	
	34	

The overall mortality was 6%; death being due either to cardiac failure or bronchopneumonia. There were no cases of gas infection.

In our hands amputation of the 1st or 5th metatarsal bone is a satisfactory method of treating perforating ulcers.

If simple amputation of the toes is carried out it is generally wise to excise also the head of the underlying metatarsal as otherwise it is apt to necrose and so delay healing.

Embolic gangrene.—Two cases were seen; one in a woman of 44. She had a below-knee amputation but died a year later from another big embolus. The other was a man aged 69 who died from a pulmonary embolus after an above-knee amputation.

Frostbite.—This case occurred in a man aged 34.

In February 1956 he was admitted to the London Hospital. He had spent three nights in an unheated attic with no overcoat. For twenty-four hours his feet had felt numb.

On the day of admission he had walked to a Salvation Army hostel and plunged his feet into hot water.

On examination.—Both feet and ankles were blue, swollen and numb. Despite treatment there was no return of circulation. Bilateral arteriograms showed a normal arterial tree to within a few inches of the ankle-joint. At that point the circulation failed. Eventually a bilateral below-knee amputation was carried out.

Pathological report.—Loss of myoglobin in muscles. Complete necrosis of small muscles of feet. Inflammation and necrosis but no thrombosis in arteries.

Such a severe degree of frostbite in a young man must be rare in this country and even rarer when it occurs in the heart of London.

Mr. Peter Martin (Hammersmith Hospital, London):

Very often the effect of anæmia in the production of symptoms in a patient suffering from ischæmia of the limb is forgotten. Its correction can be a most valuable aid in the treatment of such a patient.

We have been practising artery grafting of the peripheral vessels affected with atherosclerosis for ten years but, until recently, have been disappointed with the results. In our

earlier cases end-to-end anastomosis was largely used and the results were bad. Since we adopted the end-to-side anastomosis, putting in as it were an extra collateral, the results have been most promising and in no single instance where we have undertaken a graft have we failed to relieve the threat of gangrene. We believe it is a surgical error not to do an arteriogram in threatened gangrene from large vessel obstruction.

For the past nine months the only graft we have used in the lower limb is one from the common femoral above to the lower half of the popliteal artery below. We decided this as we have noted that although the superficial femoral artery is frequently diseased, the common femoral is rarely so severely affected. Similarly the lower half of the popliteal artery tends to escape severe disease. We have grafted with success on to a mere stump of patent popliteal artery no more than 1 in. in length, and in a patient whose peroneal artery alone was patent. When a patient has obstruction of one or sometimes two of the vessels in the leg distal to the bifurcation of the popliteal artery success may still be achieved.

As materials for grafts we have used autogenous vein, freeze-dried arterial homograft and polyvinyl alcohol sponge. Autogenous vein is successful and probably the best, but a vein of sufficient size and length to reach from the common femoral to the distal popliteal artery is not easy to get. A freeze-dried homograft is probably almost as satisfactory as autogenous vein and as this can be obtained in sufficient length we have used it extensively. In a few patients when we have not had a suitable graft available we have used polyvinyl alcohol sponge. It has remained patent long enough for gangrene to heal though there is a distinct tendency for it to thrombose after six weeks or two months. In one patient a leak occurred three months after insertion of this type of graft which demanded its removal and the insertion of a freeze-dried homograft in its stead. We no longer use polyvinyl alcohol sponge in peripheral vessel grafting.

Professor J. H. Dible (Postgraduate Medical School, London) said that there had been very little mention of the underlying pathology in these conditions. Much of the disease in the arteries fell upon the medium-sized vessels of the leg below the knee. The changes in these were commonly very widespread and extremely complex, so that the "collateral circulation", which was in fact an opening up of pre-existing vessels, especially those of the intermuscular planes, the subcutaneous tissue and the nerves, was very varied and depended upon the incidence and sites of obstruction in the larger vessels. Thus, if the anterior tibial were blocked near its origin, as is often the case, much of the blood may pass down the posterior tibial vessel as far as the middle of the leg and then, this vessel being blocked in turn, pass by anastomoses to the peroneal which might supply the foot by its anterior and posterior terminal branches. Such complicated disease in vessels of medium size did not offer much prospect of surgical intervention. A characteristic of atherosclerotic disease was the way in which smaller vessels such as the plantars and digitals escaped, whilst the main trunks in the limb were extensively diseased. In diabetes the pathological lesion in the peripheral arteries appeared to be indistinguishable in the diabetic and the non-diabetic. At the present time the speaker could find no evidence of more rapid progress of the disease in diabetic subjects: both diabetics and non-diabetics came to operation at approximately the same age.

Section of Neurology

President—D. W. C. NORTHFIELD, M.S., F.R.C.S.

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The Amyotonia Congenita Syndrome

By JOHN N. WALTON, M.D., M.R.C.P.

Neurological Unit, King's College, University of Durham, in the Royal Victoria Infirmary, Newcastle upon Tyne

EVERY pædiatrician and every neurologist must often have been faced with the problem of determining the nature of the disease process which is responsible for producing widespread and profound muscular weakness and hypotonia in an infant. The term "amyotonia congenita" has been used by many to embrace all cases of early infantile hypotonia, of whatever cause, while others, following Oppenheim's original description, have reserved this label for cases which show signs of spontaneous improvement. All too often, this difference in usage has resulted in regrettable misunderstandings, when one doctor has diagnosed amyotonia in a child with obvious spinal muscular atrophy, and another, encouraged by textbook descriptions of improvement in cases of this syndrome, has given a good prognosis, only to be proved hopelessly wrong by the course of events.

The diagnosis of amyotonia congenita, through common usage, is now generally taken to include all cases in which generalized weakness and hypotonia of the skeletal musculature is present at birth, or is noted within the first three months, and in which there is no clear evidence of any cerebral, skeletal or metabolic disorder. Admittedly, signs of brain disease or metabolic defect are notoriously difficult to elicit in the first few months of life and this is why so many cases with hypotonia symptomatic of systemic disease are initially impossible to distinguish from others with a primary neuromuscular abnormality. Having defined the syndrome it is possible to say that its causes can be divided into three principal groups which are: (1) Infantile spinal muscular atrophy and related syndromes. (2) Symptomatic hypotonia. (3) "Benign congenital hypotonia."

Before discussing the means of differentiating between cases in these groups it will be important to discuss briefly their clinical and pathological features.

(1) *Infantile spinal muscular atrophy and related syndromes.*—Werdnig (1891) and Hoffmann (1893) described the clinical and pathological features of a condition which often affected more than one member of a sibship and began usually in the second six months of life with progressive, flaccid paralysis of the limbs and trunk. The disease was invariably fatal and histological study of the spinal cord revealed that paralysis was due to extensive degenerative changes in the anterior horn cells. When, in 1900, Oppenheim described a condition characterized by a similar muscular weakness and hypotonia of onset at birth, but differing in its tendency to improvement, many authors, including Collier and Wilson (1908) seized upon the age of onset as the crucial point in diagnosing Werdnig-Hoffmann disease from amyotonia congenita. However, subsequent work revealed that most babies presenting with severe hypotonia at or shortly after birth showed the same downhill course as did typical cases of Werdnig-Hoffmann disease of later onset. In such cases the pathological changes, too, were identical (Greenfield and Stern, 1927) and hence the view became current that Oppenheim's amyotonia congenita and the Werdnig-Hoffmann disease were expressions of an identical pathological process, which in cases of the former type was present at birth, while in the latter, the condition began postnatally. Grinker (1927), on the other hand, suggested that while the abnormality in each condition was primarily one of the anterior horn cells, the former was due to a failure of development, the latter to an active degenerative process. Burdick, Whipple and Freeman (1945) believe that in amyotonia congenita there is an abnormality in development of the entire motor system, from the motor cortex to the anterior horn cells, and this view has gained a number of advocates.

These differing opinions have been considered in detail by Brandt (1950) who carried out a follow-up study of 131 cases previously diagnosed as amyotonia congenita or infantile spinal muscular atrophy. He concluded that the course and prognosis of infantile spinal muscular atrophy was not dependent upon the age of onset and within this group of cases it was not possible to identify a syndrome in which spontaneous improvement occurred, nor one in which the disease process had run its course at birth and showed no further progress. In a recent review of 30 cases, Arthuis (1954) has reached similar conclusions, as I have in a follow-up study of 67 cases reported elsewhere (Walton, 1956). It seems

probable that some cases of the condition referred to as arthrogryposis multiplex congenita (Stern, 1923) or amyoplasia congenita (Sheldon, 1932) are due to a similar spinal muscular atrophy beginning in intra-uterine life (Brandt, 1947), even though others may, as Stern suggested, be the result of a congenital limitation of joint movement, perhaps owing to excessive intra-uterine pressure. It may be suggested, therefore, that a similar disorder of anterior horn cells may give rise to the syndrome of arthrogryposis multiplex congenita if it begins early in intra-uterine life, to the initial clinical picture of amyotonia congenita if it develops at, or shortly before birth, and to the typical Werdnig-Hoffmann syndrome if it begins post-natally.

(2) *Symptomatic hypotonia.*—Diagnosis is complicated even further by the fact that a variety of other disorders may give rise to symptomatic muscular hypotonia in infancy. These causes have been discussed in detail by Brandt (1950), by Tizard (1954), and by Sandifer (1955). A number of the disorders which may present in this way are listed in Table I. Many of them were represented in the 25 cases of symptomatic hypotonia which emerged from my follow-up of 109 cases of the amyotonia congenita syndrome (Walton, 1956).

TABLE I.—THE CAUSES OF SYMPTOMATIC HYPOTONIA

(1) *Neuromuscular and muscular disorders:* Progressive muscular dystrophy, Myasthenia gravis, Polymyositis, Infantile polyneuritis.
(2) *Cerebral disorders:* "Cerebral palsy" (flaccid diplegia, congenital athetosis), Cerebral birth injury, Mental defect, Kernicterus, Cerebral lipidosis.
(3) *Nutritional and metabolic disorders:* Rickets, Scurvy, Cretinism, Malnutrition, Cœliac disease, Glycogen storage disease, Chronic infection; or following an acute illness.
(4) *Skeletal disorders:* Osteogenesis imperfecta, Arachnodactyly.
(5) *Other disorders:* Congenital heart disease, Other congenital abnormalities, Spinal cord birth injury.

The clinical features of symptomatic hypotonia. A proportion of cases of the Duchenne or pseudohypertrophic type of muscular dystrophy may show signs of muscular weakness during the first year of life. In only a few of these is hypotonia with excessive mobility at the joints a striking feature, but I have seen at least 3 cases in which this was true. Each of these children was limp and floppy as a baby and tended to "slip through the hands"; they were late in walking and did so clumsily with frequent falls. As they grew older pseudohypertrophy of the calves appeared and progressive deterioration was apparent, but in the beginning, in the absence of a positive family history, accurate diagnosis on the basis of clinical findings alone was virtually impossible. I have seen only 1 case of polymyositis in infancy and few have been described (Bovet, 1936); although this condition may give generalized muscular hypotonia, signs of constitutional upset and of muscular tenderness with subsequent induration and fibrosis of muscles are generally apparent in cases occurring at this age and act as valuable distinguishing features. In myasthenia gravis, too, the ptosis and other evidence of involvement of the cranial musculature, signs which are usually apparent even in infancy, may, when added to evidence of general muscular weakness, be sufficient to demand a therapeutic test with Tensilon or Prostigmin. Polyneuritis in infancy appears to be a rare disease, even though Adams, Denny-Brown and Pearson (1953) considered that this condition may account for many recoveries from so-called amyotonia congenita; I have no personal experience of this condition, and I was unable to find a single case in the records at The Hospital for Sick Children, Great Ormond Street, over a twelve-year period. However, I should imagine that in cases of this type, the muscular weakness and hypotonia would often show a relatively rapid onset, that there might sometimes be evidence of ascending paralysis, and that the cerebrospinal fluid protein would be raised. Three possible cases of infantile polyneuritis giving the clinical picture of amyotonia congenita have been described by Chambers and MacDermot (1957).

In the various cerebral disorders which may be accompanied by severe muscular hypotonia, any infant which is found to have hypotonic musculature following prolonged cyanosis after a difficult labour, may be presumed to have a cerebral birth injury, particularly if other evidence of brain damage is present. The infant with cerebral palsy, too, may have remarkably limp and flaccid limbs, and may show a striking delay in the development of motor skills, while unusual posturing of the limbs with rather sinuous movements may herald the development of athetosis. Generally, in such cases the tendon reflexes are retained or even unusually brisk, and the plantar responses may remain unequivocally extensor long after the usual age. Similar features usually become evident in case of cerebral lipidosis which may also be generally hypotonic in the beginning, but subsequently epileptic manifestations and particularly myoclonus on startle, usually develop. In kernicterus, too, there may be a history of prolonged neonatal jaundice, while associated deafness and evidence of rhesus incompatibility may be invaluable distinguishing features.

Finally in this group we must mention the mentally defective child, whose limbs are often limp and unusually mobile on passive movement, and whose delay in motor development may be much more striking than his relatively slight mental backwardness. The diagnosis of minor degrees of mental defect in infancy can be a matter of the greatest difficulty and may call upon all the pædiatrician's reserves of skill and experience in assessing the infant's behaviour against a background of known variations in normal development.

When one comes to consider the various nutritional and metabolic disorders which I have listed, it is almost possible to dismiss rickets as a disease which no longer occurs in this country, except in infants with renal disease. Usually in this entire group of cases it is apparent that the muscular weakness and hypotonia which the infant shows is a relatively secondary feature and is overshadowed by fever, by wasting or by some other striking features of systemic disease. When generalized hypotonia develops after an acute illness, rapid recovery is usually the rule, but when the condition is more prolonged, careful attention to the dietary history, urinalysis, examination of the stools, radiographs and biochemical studies, revealing perhaps hypercalcæmia or urinary infection with nephrocalcinosis, may solve the problem. The diagnosis of cretinism, too, will rarely present much difficulty to the experienced pædiatrician after the first few weeks of life. It is in the less common cases where muscular hypotonia is the presenting feature, overshadowing the evidence of general disease, that difficulty arises. I remember, for instance, twin baby girls whose limbs were limp and flabby and who made no attempt to sit between the sixth and ninth months of life. They were also somewhat miserable and tended to cry whenever their limbs were handled. It was only after radiographs of the limbs had revealed subperiosteal thickening that it was discovered that these children were suffering from scurvy; their muscular hypotonia disappeared rapidly after treatment with ascorbic acid. In a similar case which I saw during 1955, a boy aged 14 months had strikingly weak and mobile limbs (particularly the legs), could only sit with difficulty and had made no attempt to stand. He also had an enlarged liver and spleen and was found to be a case of glycogen storage disease. It must be mentioned, however, that in some cases of this type there is no hepatomegaly or splenomegaly as the disorder of glycogen storage is confined either to the muscles—when the diagnosis may only be made by histochemical studies of muscle removed by biopsy—or to the ganglion cells of the central nervous system (Clement and Godman, 1950; Krivit *et al.*, 1953).

Among the skeletal conditions which may be associated with muscular hypotonia is osteogenesis imperfecta; in late infancy this condition may present with flabbiness and undue mobility of the limbs but the family history and subsequent development of fractures will generally lead to the correct diagnosis being made. In arachnodactyly, muscular hypotonia is generally slight, though the limbs may always seem to be unusually mobile; here the diagnosis will be made on the appearance of the digits, on the family history and the association of other defects such as arching of the palate or cardiac abnormalities. It should also be remembered that some infants with congenital heart disease (particularly the tetralogy of Fallot) may be limp and flabby, as may others with multiple congenital abnormalities, of, say, heart and skeleton. The diagnosis of the rare spinal cord birth injury is not generally difficult to make, as there is generally severe flaccid paralysis of the lower limbs only, often with sensory loss. And finally, in considering the causes of symptomatic hypotonia, the possibility of misinterpretation of physical signs should be remembered; in some cases of bilateral congenital hip dislocation, for instance, the comparative immobility of the lower limbs may be wrongly attributed to muscular weakness.

(3) *Benign congenital hypotonia.*—This third and smallest group of cases is for many reasons the most important, since in these children the muscular weakness and hypotonia, though initially profound, resolves gradually and a significant proportion of the patients recover completely, without showing signs of any cerebral, metabolic or skeletal disorder. In a follow-up study of 109 cases previously diagnosed as amyotonia congenita, I found (Walton, 1956) that 17 proved to be of this type; these cases have been reported in detail (Walton, 1957). 8 of them (3 male, 5 female) had recovered completely and 9 (4 male, 5 female) had improved but showed some degree of residual disability. Subsequently, I have observed 2 additional cases which I shall describe briefly as illustrative of the condition.

Case I.—J. N. was first seen in 1952 at the age of 18 months. She was born at term by a normal delivery and seemed to thrive but it was soon apparent that all her limbs were limp and "floppy", that they could be placed in unusual positions, and that she tended to "slip through the hands". She made no attempt to sit until she was just over a year old and when seen aged 18 months she was unable to stand, and her trunk seemed to slump when she sat on the floor. There was severe generalized muscular hypotonia but nevertheless spontaneous movements of the limbs were quite good and the tendon reflexes were present. A provisional diagnosis of amyotonia congenita was made. The child was not seen again until 1956. Soon after the previous attendance she had begun to improve and had walked alone, though clumsily and with frequent falls, shortly after she was 2 years old. Improvement thereafter was rapid; on examination in late 1956 at the age of

6 years she walked and ran briskly, hypotonia had disappeared, and it was apparent that she had recovered completely.

Case II.—R. K. was first seen in 1952 at the age of 12 months and then presented a clinical picture similar to that described in J. N. After a normal birth the child appeared to thrive but it was subsequently noted that he moved very little and was limp and "floppy". On examination he was unable to sit; all movements of the limbs were weak, there was a profound generalized hypotonia with striking hypermobility of the joints, and the tendon reflexes were generally depressed. A diagnosis of amyotonia congenita was made; despite the absence of fasciculation of the tongue and although respiratory movement was reasonably good, it was thought that the child might turn out to be a case of progressive spinal muscular atrophy. Subsequently, however, he showed slow improvement, was able to sit at 18 months and took a few steps unaided when nearly 3 years old. When re-examined at the age of 5 he walked reasonably well with slight accentuation of the lumbar lordosis but was unable to rise from the floor without making use of his hands. There was a slight thoracic scoliosis. All the skeletal muscles were unusually small and weaker than the normal; this atrophy and weakness, though not showing the typical selectivity of progressive muscular dystrophy, affected sternomastoids more than the posterior neck muscles and proximal limb muscles more than the distal. Muscular hypotonia and joint hypermobility persisted, particularly at the hips and wrists, but the deep tendon reflexes were all present and equal. Electromyography and muscle biopsy were not performed. This child has shown slow but steady improvement since the age of 3, but from my experience of other similar cases I doubt whether he will recover completely.

These 2 cases illustrate very well the salient features of the syndrome of benign congenital hypotonia and these are summarized in Table II, in which information from the 17 cases previously described is also included.

TABLE II.—THE CLINICAL FEATURES OF BENIGN CONGENITAL HYPOTONIA

	Muscular weakness and atrophy	Hypotonia and joint hypermobility	Respiratory muscle involvement	Tendon reflexes	Prognosis
(*a*) Cases with complete recovery	+	++	−	Normal or depressed	Complete recovery 5–12 years
(*b*) Cases with incomplete recovery	++	+++	±	Depressed or absent	Persisting muscular weakness, atrophy and hypotonia particularly of proximal limb groups

In all cases the EMG was "myopathic" and muscle biopsy was normal

In summarizing the clinical features as I have observed them I think one can say that babies in both groups show a reduction in spontaneous movements of the limbs in addition to generalized hypotonia and an increased range of passive movement of the joints, but that each of these features is of greater severity in the cases which show incomplete recovery. Similarly, respiratory muscle weakness is seen only in the severe cases, in which depression of the tendon reflexes is also more severe. When I say that electromyographic tracings are "myopathic" I mean that in the cases which I have examined, the interference pattern on voluntary effort showed excessive polyphasic and short duration potentials, as seen in myopathic disorders. This finding, which clearly requires confirmation and amplification in future studies, does not necessarily imply an active myopathic process, but may simply mean that many motor units are populated with less than the normal number of muscle fibres. Turning to the muscle biopsy findings, it is true that in 6 of the cases which I have seen, specimens of muscle obtained at biopsy showed no abnormality when stained with conventional techniques. It is worth noting, however, that Coërs and Pelc (1954) and Woolf and Till (1955), who have each studied single cases which may be of this type, using intravital staining of motor end-plates with methylene blue, found that the end-plates were "immature".

Considering now the relationship of benign congenital hypotonia to other conditions previously described, I believe that many of the cases described by Sobel in 1926 under the title of "essential or primary hypotonia" were of this type. Some of his cases, however, were probably examples of "congenital laxity of the ligaments", which seems to be a separate disorder, since it is often inherited, and the excessive mobility of joints (as seen in contortionists) persists throughout life, but there is no muscular weakness, delay in development, or physical handicap. The cases which recover incompletely are strikingly reminiscent of the "benign congenital myopathy" described by Turner (1940, 1949) save for the fact that his patients showed a selective muscular atrophy like that of muscular dystrophy and in one of them pathological changes in the muscle were found which were

interpreted as myopathic in type. However, it seems possible that these pathological changes, consisting of areas of focal degeneration and phagocytosis of muscle fibres, were related to the terminal illness, namely bacterial endocarditis, from which the patient died after a long period in bed; changes of this type are usually seen only in rapidly progressive cases of muscular dystrophy and would be unexpected in a benign, long-standing myopathic disorder. My cases with residual disability show an even closer resemblance to the condition of "congenital universal muscular hypoplasia" described by Krabbe (1946) and Ford (1952). I have given reasons (Walton, 1957) for suggesting that Turner's "congenital myopathy", Krabbe's "universal muscular hypoplasia" and "benign congenital hypotonia with incomplete recovery" must be closely related, if not identical.

When we come to consider the ætiology of this clinical syndrome, the findings of Coërs and Pelc (1954) and of Woolf and Till (1955) suggest that in certain cases it may be due to an immaturity of the neuromuscular apparatus, which is sometimes overcome by the processes of postnatal development but in other patients is too severe for this natural adjustment to occur. There are, however, many other possible explanations which require exploration by means of electrophysiological, biochemical and neuropathological techniques. I should prefer to conclude by considering briefly some of the principles of differential diagnosis in cases of infantile hypotonia.

Differential Diagnosis

From the point of view of the practising physician, this is the most important problem of all and it is one which bristles with difficulties. If the prognosis is to be foretold with any degree of confidence, it is essential to decide at the earliest possible moment whether the child is suffering from spinal muscular atrophy, from symptomatic hypotonia, or from the syndrome of benign congenital hypotonia. If the diagnosis is spinal atrophy then the prognosis is grave and treatment of no avail; if symptomatic hypotonia, the prognosis is that of the underlying condition, for which specific treatment may be required; while if benign congenital hypotonia is diagnosed a guardedly favourable prognosis may be given until it becomes apparent whether the child will recover completely or incompletely, and in the meantime physiotherapeutic supportive measures and appliances to prevent deformities (such as spinal jackets in occasional cases) may be needed. In Table III I have tried to bring together a number of the points which may aid in differential diagnosis.

Table III.—The Differential Diagnosis of the Causes of Infantile Hypotonia

	Muscular weakness and atrophy	Hypotonia and joint hypermobility	Respiratory muscle involvement	Fasciculation of tongue and bulbar involvement	Contractures and skeletal deformity	Tendon reflexes	Signs of other systemic disease	EMG	Muscle biopsy	Natural history
Spinal muscular atrophy	+++	+++	++	+	++	−	−	Neuropathic	Denervation atrophy	Progressive
Symptomatic hypotonia	±	+(+)	−	−	±	+	+	Often normal, or else that of the primary disease		That of the primary disease
Benign congenital hypotonia	++	++	±	−	±	±	−	Myopathic	Normal	Improvement

Muscular weakness and atrophy are, of course, most severe in the cases of spinal muscular atrophy; although in the infant this atrophy may be concealed by adipose tissue, it can often be demonstrated by soft-tissue radiographs. The characteristic picture of the virtually immobile child, who lies with the arms abducted and externally rotated and with hips abducted and knees flexed, scarcely moving except to breathe, is very characteristic. On being lifted the child is limp and unresisting, tending to slip through the hands, the so-called "rag-doll" baby. Although weakness, hypotonia, and a very obvious increased range of passive movements at the joints are equally a feature of children with benign congenital hypotonia, children in the latter group always show some spontaneous mobility of the limbs and are never so completely paralysed as the severe cases of spinal muscular atrophy. In cases of symptomatic hypotonia, weakness and hypotonia are usually even

less; nor do these cases show respiratory muscle involvement, with recession of the lower ribs at the diaphragmatic attachment during inspiration, a feature which is sooner or later invariable in cases of spinal muscular atrophy and only occurs to a limited extent in the most severe cases of benign congenital hypotonia. Fasciculation of the tongue, too, and other evidence of bulbar involvement such as pooling of secretions in the pharynx, occur only in cases of the Werdnig-Hoffmann type. In similar cases which survive into the second year of life, muscular contractures and severe skeletal deformities, secondary to muscle weakness, invariably develop. Such phenomena are uncommon and relatively slight in cases of symptomatic and benign hypotonia. Furthermore, depression of tendon reflexes is most severe in cases of the anterior horn cell disease, and is less striking in examples of benign hypotonia, while in many of the symptomatic cases the reflexes are normal or even unusually brisk. Also, as I have mentioned, in cases of the latter type there may be signs which indicate the nature of the primary condition, of which generalized hypotonia is but a symptom.

So far as investigations are concerned, the electromyogram in spinal atrophy may show spontaneous fibrillation in a considerable proportion of cases, while volitional activity usually takes the form of repetitive large and broad motor unit potentials; in symptomatic hypotonia the record will generally be normal. My findings suggest that in benign congenital hypotonia the interference pattern of voluntary effort will often show excessive polyphasic and short duration potentials, similar to those seen in myopathic disorders. However, it should be remembered that electromyography may be difficult to carry out satisfactorily in young infants. Muscle biopsy, on the other hand, may be of the greatest value, since in spinal muscular atrophy it will reveal the characteristic atrophy, in groups, of muscle fibres, which is characteristic of denervation, while in the other two groups of cases muscle specimens when studied with conventional techniques will usually be normal, except when the hypotonia is symptomatic of some other muscular disease. Finally, we must mention that the natural history of the illness will eventually make diagnosis certain, as cases of spinal atrophy will become progressively weaker, those of benign hypotonia will improve, and in those with symptomatic hypotonia the nature of the underlying disease will surely become apparent.

I do not wish to imply, by formulating these principles of differential diagnosis, that it is an easy matter. In many cases it will be impossible to be certain of the true state of affairs after a single examination and it may be necessary either to await the course of events, a decision which will inevitably cause some distress to the child's parents, or to arrange investigations in hospital, in the hope of reaching an early decision. Even then there will undoubtedly be difficult cases in which only time and repeated observation will solve the problem; but I hope that some of the information I have given may be of help in allowing an accurate prognosis to be made earlier in an increased proportion of cases.

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Dr. **J. G. Greenfield** congratulated Dr. Walton on his clarification of what had been a very confused subject. In his opinion this confusion was chiefly due to Oppenheim, who had diagnosed as myatonia congenita many cases which later progressed and on pathological examination showed the lesions described by Werdnig and Hoffmann. On reviewing the literature in 1927 (*Brain*, 50, 652) he found that in all except two of the fatal cases, in which the diagnosis of amyotonia congenita had been made up to that time, the lesions were identical with those of the Werdnig-Hoffmann type of paralysis. In the other two cases the clinical features indicated a central lesion of the brain or cerebellum. But at that time he was aware of the familial cases later published by Dr. Aldren Turner. In 1955 he had seen two cases in the United States which corresponded to Dr. Walton's description of benign congenital hypotonia. In both cases the proximal muscles were chiefly affected and in both, muscle biopsy showed quite normal muscle. Biopsy was a valuable aid to diagnosis and prognosis, but it must be remembered that in very young infants all the muscle fibres were of small size, otherwise there might be confusion in the interpretation of the histology. He agreed with Dr. Walton that the name "Amyotonia congenita" should be dropped and the name "Benign congenital hypotonia" used for cases of this kind.

Dr. **A. L. Woolf** said that Oppenheim (1900), in an admirably concise report headed "Myatonia in Early Childhood", had drawn attention to a number of infants he had seen, who showed a remarkable degree of hypotonia or even atonia, which seemed to date from birth. Several of these children had improved in the course of time and Oppenheim, therefore, believed the condition resulted from a retardation in development of muscle or anterior horn cells, rather than an acquired disease of the nervous system.

From a study of the literature, it seemed clear that most of the confusion over the relationship of amyotonia congenita to Werdnig-Hoffmann disease had resulted from the difficulty in distinguishing the two conditions by clinical examination alone. Oppenheim (1908) recognized this and emphasized the importance of the clinical history. He was no doubt referring to the early onset and tendency to spontaneous improvement which were characteristic of the cases he was describing. It was possible that Oppenheim did not realize that Werdnig-Hoffmann disease could manifest itself in the first six months of life, but as far as the written word was concerned it appeared that we must hold Rothmann (1909) responsible for the suggestion that congenital cases might be considered as Oppenheim's disease and cases of later onset as of the Werdnig-Hoffmann type. This suggestion, unfortunately, appeared to have been adopted, and the morbid anatomical basis of Oppenheim's disease deduced from histological examination of spinal cords from cases which were really examples of Werdnig-Hoffmann disease, true cases of amyotonia congenita, by their very nature, being unlikely to come to post-mortem examination. It was little wonder that it became accepted that the anatomical basis of amyotonia congenita and Werdnig-Hoffmann disease was the same and that they were, in fact, one and the same disease.

Henceforth, the two terms were used interchangeably. Dr. Walton had more sharply defined the clinicopathological entity of Werdnig-Hoffmann disease and emphasized that it might have a congenital or even antenatal, onset. He had shown some of the remaining cases might be due to a variety of causes, including a group which could not at present be further broken down and which resembled closely those described by Oppenheim as myatonia congenita. Dr. Woolf suggested that these cases were, in fact, examples of Oppenheim's disease that Dr. Walton had rescued from the miscellaneous group of infantile hypotonias, amongst which their special nature had for so many years been lost sight of, owing to the indiscriminate application to all the cases in the group, of the term amyotonia congenita. Dr. Woolf further suggested that, henceforth, recognition should be given to Oppenheim's service in drawing attention to the congenitally floppy baby with good prognosis, by retaining his term myatonia congenita or amyotonia congenita, but that it should be made clear that not every case of hypotonia, with a congenital or antenatal onset, fell into this group.

With the possibility of diagnosing amyotonia congenita in life, the opportunity of defining the changes in the muscle and intramuscular nerve endings by muscle biopsy became more favourable and might thus result in a useful diagnostic aid.

Dr. Woolf briefly described three cases. The first (case of Dr. B. S. B. Wood), a child of 10 months with the clinical features of amyotonia congenita, showed a muscle completely normal in all respects. Bielschowsky preparations showed a rich innervation. Acetyl cholinesterase preparations showed large numbers of subneural apparatuses of end-plates, which were just as complex, though naturally smaller, than those of an adult. Vital staining with methylene blue showed end-plates only slightly less elaborate than those of a normal child aged 1 year (preparation kindly lent by Dr. C. Coërs). This child, shortly after muscle biopsy, rapidly improved, the tendon reflexes even becoming brisk. There had been a blood urea of 54 mg./100 ml. but there was no other evidence for a biochemical disorder as the basis of the condition, and at any rate, biopsy had foretold the favourable outcome.

The second child (case of Dr. H. Parry Williams), aged 2 years 4 months, also showed the clinical features of amyotonia congenita. The muscles were very slender indeed, as seen in radiographs, and there was a flexion deformity of the outer three fingers on each side. Muscle biopsy did not show any definite abnormality in hæmatoxylin and eosin preparations, but acetyl cholinesterase preparations showed few end-plates, and those present appeared to contain little acetyl cholinesterase, only a few crystals of brown staining material being present even after three and a half to twenty-four hours' incubation. Vital staining with methylene blue showed many end-plates and nerve fibres. Some of the end-plates were poorly formed or bizarre, but many were as mature as in the adult. The course of the nerve fibres across the muscle fibres was more oblique than normal, although muscle fibres had been lost. There were also some fine beaded sprouting nerve fibres. The significance of these findings was obscure but they did not strikingly suggest immaturity.

Finally, Dr. Woolf referred to a case of myasthenia gravis (Dr. E. R. Bickerstaff's case), who had always been slow in his movements, but had recently, at the age of 12 years, developed a ptosis of myasthenic type with good response to Prostigmin. Vital staining with methylene blue and acetyl cholinesterase preparations showed that, while the majority of the end-plates were of "adult" type, a minority consisted only of one to three simple spherical expansions, grouped closely together so that no terminal arborization could be seen. The significance of these immature looking end-plates is not yet clear but it is obvious that this appearance must not be regarded as diagnostic of amyotonia congenita.

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The Histochemistry of Normal and Abnormal Human Muscle

By E. B. BECKETT, B.Sc., and G. H. BOURNE, D.Sc., D.Phil.

Department of Neurology, The London Hospital and Department of Histology, The London Hospital Medical College

Introduction.—Muscle is made up of fibres, the structures (motor end-plates) which innervate them, and the connective tissue which binds them together. The fibres are themselves composed of (i) the contractile elements, and (ii) the sarcosomes which occur between them. Of the two main metabolic pathways by means of which glycogen is oxidized to produce energy the group of enzymes concerned with the anaerobic path are concentrated in the contractile portion and those concerned with the aerobic pathway in the sarcosomes.

Suitable techniques are not available for the histochemical demonstration of the first group of enzymes but techniques are available for the second, particularly succinic dehydrogenase and cytochrome oxidase which are largely concentrated in the sarcosomes; and these were among those used in this study. It was thought that as well as making a study of the enzyme activity of these bodies, observations should also be made of their general shape and appearance.

MATERIAL

Controls.—In this work controls were obtained at one-hour *post mortem* from two young healthy adults and four specimens were obtained within twelve hours of death from elderly people. A few control specimens of doubtful value were also obtained—one was taken during a cup arthroplasty (in this the muscle was definitely abnormal) one was taken at amputation of a limb which had been immobilized by accident and disease for twenty-five years (in this the muscle showed simple atrophy), and some specimens were also taken from the abdomen at operation.

All diseased muscle used for comparison with these controls was taken by biopsy and was put straight on to solid carbon dioxide in a sealed glass jar. The histochemical techniques were usually commenced on such samples of muscle within fifteen minutes of its removal from the body. All biopsy specimens were taken from the motor point as indicated by surface and direct faradic stimulation. The muscle chosen for biopsy was one in which functional changes were rapidly taking place. The diseases from which biopsy material was obtained included: facio-scapulo-humeral dystrophy, pseudo-hypertrophic dystrophy, familial dystrophy, polyneuritis, polymyositis, motor neurone disease, peroneal muscular atrophy, several neuropathies and myopathies of unknown origin, carcinomatous neuropathies and myopathies.

RESULTS

Sarcosomes.—A. *Structure.*—Heidenhain's iron hæmatoxylin method was used to demonstrate the sarcosomes. In rat muscle a number of elongated structures were found to be demonstrated by this method, and in human muscle many small rounded structures were seen. Some doubt was felt as to whether these structures were, in fact, sarcosomes. In a number of specimens of dystrophic muscle these rounded structures did not appear to be demonstrated and in many cases they appeared to form elongated strands of material which took up the stain strongly. However, similar structures were found in normal muscle which had been subjected to trauma. But this condition was found more often in dystrophic than in normal muscle, which suggests that if it is due to collapse of the sarcosomes, then the latter are more fragile in dystrophic muscle. This problem cannot be adequately solved until the precise identity of the hæmatoxylin-staining structures are known, and this will require electron microscopy.

B. *Enzymes.*—A histochemical test for succinic dehydrogenase was used, the technique being that of Seligman and Rutenburg (1951) as modified by Shelton and Schneider (1952).

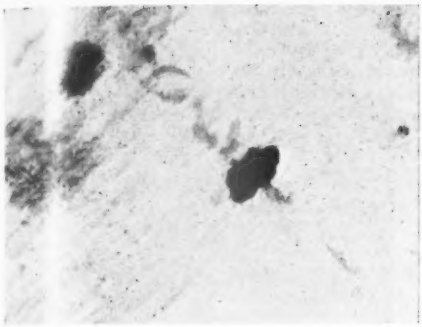


FIG. 1.

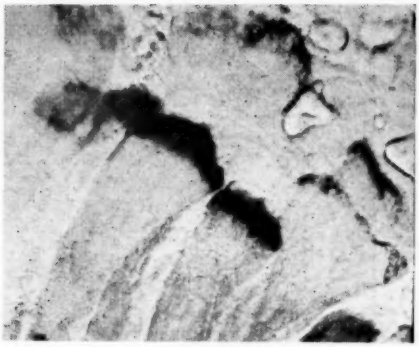


FIG. 2.



FIG. 3.

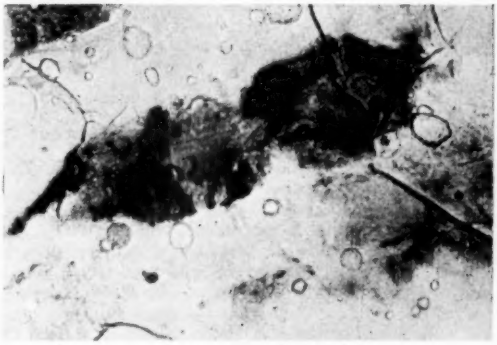


FIG. 4.

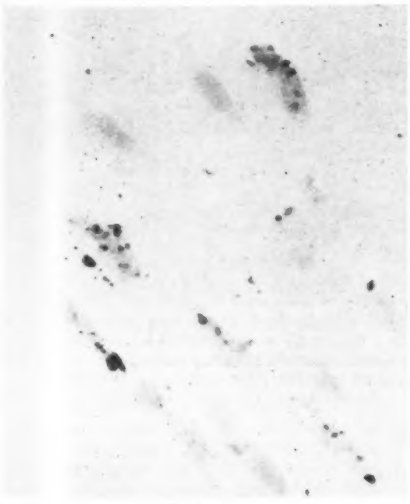


FIG. 5.

FIG. 1.—Acetyl cholinesterase in "classical" motor end-plate found in muscle taken from a case of motor neurone disease. × 1,000.

FIG. 2.—Acetyl cholinesterase in musculo-tendinous junctions. × 150.

FIG. 3.—Very extended end-plate from a case of familial muscular dystrophy. × 100.

FIG. 4.—Disrupted end-plate from a case of pseudo-hypertrophic muscular dystrophy. × 150.

FIG. 5.—Very atrophied muscle fibres in a sea of dense connective tissue taken from a case of facio-scapulo humeral dystrophy. Note the many remaining end-plate structures. × 150.

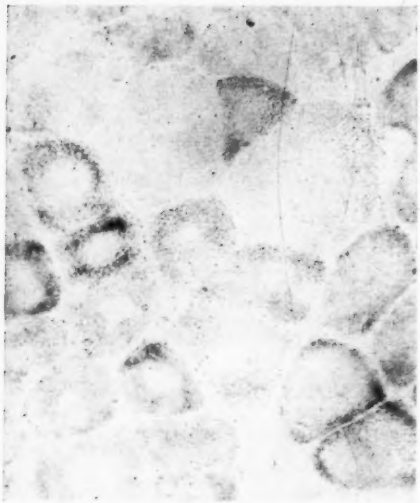


FIG. 6.—Succinic dehydrogenase in muscle from a case of polymyositis. Some large fibres have a weak reaction, whilst the smaller ones have a broad peripheral band of strong reaction. × 120.



FIG. 7.—Succinic dehydrogenase in muscle fibres, showing aggregation of diformazan granules along the sarcolemma. × 208.



FIG. 8.—5-nucleotidase in muscle from a case of ? pseudo-hypertrophic muscular dystrophy ? polymyositis, showing highly enzyme-active cells invading a very atrophied fibre which itself shows a positive reaction. × 416.

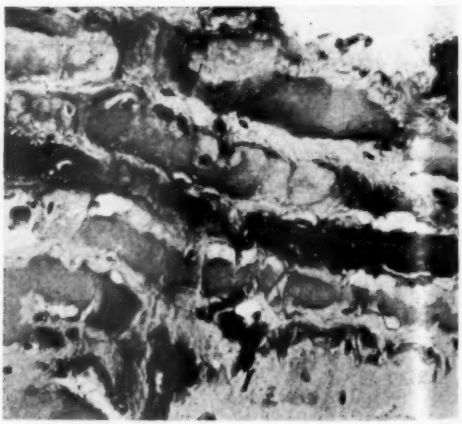


FIG. 9.—Muscle from a case of familial dystrophy, showing a large concentration of 5-nucleotidase in connective tissue fibres, in invading cell nuclei and in some atrophied muscle fibre. × 160.

In normal human muscle there was considerable variation in the intensity of the reaction. This was due partly to a random variation from unknown causes and partly to the fact that the reaction varied quite considerably in different muscles. The succinic dehydrogenase activity varied quite independently of the cytochrome oxidase. In general, we found that the intensity of the reaction tended to be decreased in pathological muscle, indicating a lower aerobic metabolism, but it was not possible to find any correlation with clinical diagnosis. In cases where the muscle was largely replaced by connective tissue there was, as might be expected, a very considerable reduction of the reaction.

Fibres.—The structure of the contractile elements could not be investigated without facilities for electron microscopy which we did not possess and suitable techniques were not available to study the enzymes located in them which are concerned with anaerobic respiration.

Motor end-plates.—An investigation of the structure of these bodies was not carried out but a study of their cholinesterase activity was made. The technique used did not employ formalin fixation. This type of fixation has been used by other authors but we felt that it should not be used in the present work since it is known partially to inhibit the enzyme in many tissues (Taxi, 1952, and Couteaux and Taxi, 1952) and we have shown it to inhibit completely the reaction in human fœtal muscle. The technique used was Gomori's (1952) modification of Koelle and Friedenwald's (1949) method and the specificity of the reaction was controlled by the use of eserine.

Two types of cholinesterase-positive structure have been found in human muscle (Coërs, 1953 and 1955). These are the type known as the "classical" end-plates or "terminaisons en plaque" and the "terminaisons en grappe". The first of these consists of a ribbon-like gutter structure twisted upon itself; and the second of small round gutter structures grouped together without any particular connexion between them and often covering an area of considerable size. This latter type seems to be characteristic of human muscle and does not appear to occur in the muscles of experimental animals. Two other cholinesterase-positive structures which have been found are the motor end-plates which occur at each end of the intra-fusal fibres of muscle spindles, and structures situated at the ends of the muscle fibres at the musculo-tendinous junctions, described by Couteaux in 1953 in frog, mouse and fish and by Gerebtzoff (1956) in the muscles of a variety of animals including humans. All of these structures have been seen in the human muscle which we examined, the "classical" plates usually being found to be arranged in rows across the muscle.

We very rarely found any decrease in the cholinesterase activity of any of these structures in pathological conditions. However, in muscle from a case of peroneal muscular atrophy and one from a case of polyneuritis there was some decrease in the reaction intensity in cholinesterase-positive structures at the musculo-tendinous junctions.

We found perfect "classical" end-plates with full cholinesterase activity in muscle obtained from a case of motor neurone disease. In several pathological muscle specimens some previously undescribed cholinesterase-positive structures were found. For example, objects consisting of parallel gutters arranged like a "cake-frill' 'could be seen. These appeared to be normal structures although we have not so far observed them in normal specimens of human muscle. It is possible that they represent some type of stretch receptor. A structure composed of a "shower" of parallel gutters was also seen, and one which in cross section appeared to be in the form of a gutter wound spirally round a muscle fibre. In the piece of iliacus muscle taken from a patient undergoing cup arthroplasty for osteoarthritis there were areas containing small "dots" of cholinesterase activity and in many cases the muscle fibres appeared to possess enzyme activity diffused through the substance.

One of the most striking observations which have been made in this work is that in some cases where most of the muscle has been replaced by connective tissue (for example, in familial muscular dystrophy) remnants of muscle fibres can be seen floating in a sea of connective tissue but possessing end-plates which appear normal in structure and possessing undiminished enzyme activity. In fact, one gains the impression that the possession of cholinesterase activity within a gutter-like structure retards the destruction of that particular area of muscle. It is of interest, however, that when muscle fibres are undergoing atrophy (but not simple atrophy) they appear to develop considerable diffuse cholinesterase activity. Even normal human muscle fibres contain a certain amount of diffuse cholinesterase activity (inhibited by eserine)—a fact which is not recorded by other authors.

Connective tissue.—The connective tissue of muscle has been thought of largely as a structural component and to have function only in the sense that it serves as a support for the nerves and blood vessels which supply the muscle fibres. The results obtained in this work suggest, however, that it may play a very active part in the development of many dystrophies.

This has been shown by the use of a technique which demonstrated the enzyme 5-nucleotidase. The technique was that of Gomori (1952). This enzyme splits muscle adenylic acid, which is adenosine monophosphate, and which is used as a starting point for the re-synthesis of A.T.P.

When this technique is applied to normal human muscle there is very little reaction shown by any of the tissue elements with the exception of the walls of the larger blood vessels and nerve fibres. In one sample of control muscle where there were signs of inflammation, the inflammatory cells gave a positive reaction. However, it was found that about one-quarter of the pathological specimens examined showed a great increase in the reaction for this enzyme in the connective tissue, particularly in cases of muscular dystrophy characterized by atrophy of fibres and increase of interstitial connective tissue. This was also found in one case of myopathy and one of motor neurone disease. In other pathological specimens there was only a small increase in enzyme activity. There was no correlation between the increased occurrence of this enzyme and the type of clinical diagnosis. Muscle fibres which were undergoing degenerative atrophy were found to have this enzyme diffused through the atrophying portion. In the connective tissue, fibres, cells and capillaries appeared to be invading and destroying the muscle fibres, and each of these elements gave a strong 5-nucleotidase reaction.

It appears from this that one of the features of many dystrophies is active physical and chemical destruction of the muscle fibres by the connective tissue which normally supports and nourishes it, and it seems possible that some inhibitory substance for this enzyme might find a place in the treatment of dystrophies.

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Dr. A. L. Woolf in discussion on Dr. Bourne's paper said that some of the subneural apparatuses in acetyl cholinesterase preparations, with an increased number of small, darkly staining elements, resembled those he had seen in cases with evidence of reinnervation in methylene blue preparations.

Dr. H. S. Baar asked Dr. Bourne what tetrazolium salt he had used. In his experience for quantitative estimation of succinic dehydrogenase in tissue homogenates in the presence of an excess of substrate only mono-compounds were useful. For histochemical demonstration best results were obtained with bis-compounds, particularly with the blue tetrazolium. The blackish-blue diformazan at sites of high activity contrasted beautifully with the red monoformazan at sites of low activity. The small size of crystals permitted also the localization of succinic dehydrogenase in sarcosomes. What was Dr. Bourne's experience on the glycogen content of muscles in cortisone-treated myopathies? The speaker had the opportunity to examine a fatal case of dermatomyositis which had been treated with cortisone and prednisolone for one year. Active muscles contained little glycogen but the soleus muscle which was inactivated because of fibrous contracture of knees and showed no fibrous replacement was studded with innumerable granules of glycogen. Even in the gastrocnemius, which showed advanced fibrous replacement, fragments of the degenerated muscle were recognizable as short cylindrical accumulations of glycogen within fibrous tissue.

Dr. J. N. Walton said that Dr. Bourne and Miss Beckett had mentioned the hypertrophied muscle fibres which they saw very commonly in their cases of muscular dystrophy. Did their observations indicate the nature and cause of this hypertrophy; for instance, did the enlarged fibres contain more than the usual complement of fibrils? Did the histochemical studies give any explanation for the remarkable accumulation of fat which appeared between the fibres in some cases of muscular dystrophy; this infiltration often appeared to be far greater than would be necessary for simple replacement of atrophied muscle. Lastly, had Dr. Bourne and Miss Beckett discovered any essential histochemical differences between different muscles or muscle groups? It was very difficult to explain the curiously selective muscular involvement which occurred in muscular dystrophy on the basis of a diffuse biochemical disturbance.

Miss Beckett and **Dr. Bourne,** in reply to Dr. Woolf: The presence of a large number of small darkly-staining elements in an end-plate area is not necessarily indicative of re-innervation (Coërs, 1955).

In reply to Dr. Baar: We used neotetrazolium. We have found histochemically that there is a large variation in the amount of glycogen normally present in muscle. If cortisone had any effect it was not observable in our specimens.

In reply to Dr. Walton: We did no counts of myofibrils, but they did not appear to be increased in size, so that they may be increased in number. We cannot account for the gross increase in fatty tissue observed in some muscular dystrophies.

We have observed some histochemical differences between different muscles and muscle groups. The most striking is the difference observed in succinic dehydrogenase levels.

Section of Odontology

President—J. A. S. WRIGHT, A.F.C., F.D.S. R.C.S.Eng., H.D.D., F.D.S. R.C.S.Ed.

[*January* 28, 1957]

Muscles and the Teeth

By W. J. TULLEY, B.D.S., F.D.S. R.C.S., D.Orth.R.C.S.

The Dental School, Guy's Hospital

IN recent years much has been written concerning the role of the muscles activating the jaws and surrounding the dental arches; it is convenient first to review some of the basic anatomical and physiological concepts. Muscle is not as responsive to its environment as bone. Bone is constantly being remodelled but the number of fibres in any muscle is fixed. A muscle can only increase in size by hypertrophy as occurs in the leg muscles of athletes but the latter show no significant increase in the size of their bones. The shape and arrangement of a muscle varies considerably from one individual to another.

A skeletal muscle is part of a functional system and never acts as a separate unit; it may be a prime mover, an antagonist or a synergist. Many activities do not normally enter consciousness, movements follow a stimulus as a patterned behaviour. In man, the progressive domination of motor reactions by the highest functional levels of the central nervous system is of considerable significance. Disharmonies in the conscious levels of the mind may be a common source of motor disability and faulty posture and uneconomical use of various muscles may arise due to this.

If a man suffers paralysis of a flexor muscle group, an extensor muscle can be transplanted on to the flexor surface and the function re-learned until a new pattern becomes established. One of the controversial aspects of adverse muscular behaviour related to the masticatory and circumoral muscles has been the statement that their basic patterns of motor activity cannot be changed (Ballard, 1955).

If we apply general principles to our particular field we see that some of the functions of the orofacial muscles are functionally represented at a much higher level in the brain than others. Activities such as swallowing are only under voluntary control in the first stage. Swallowing is a basic reflex behaviour initiated even before birth and it is not unreasonable to infer that changes cannot be readily established by exercises.

Activities such as speech have a high degree of cortical control. It is true to say that some speech defects are due to abnormal neuromuscular anatomy but many are due to defects in learning and are re-educable by conscious effort.

Mastication occupies a position between the function of swallowing and speaking. It can be compared with walking. Each individual develops a characteristic subconscious chewing "gait". This is built up on an underlying co-ordinating pattern in the nervous system but will vary considerably with the anatomical position of the teeth. Abnormal tooth position will be reflected in the masticatory pattern.

Research methods used to investigate normal and abnormal muscular activity in relation to the teeth can be divided into the following groups:

(1) Clinical observation over a long period. This may be recorded by cine film.
(2) Animal experimentation (surgical intervention with unilateral muscle function).
(3) Observations of the effects of pathological conditions affecting muscle function.
(4) Cine fluoroscopy of the soft tissues.
(5) Electromyography and methods of recording muscle forces.

CLINICAL OBSERVATIONS

Most of the valuable contributions to our knowledge of orofacial behaviour have been made by astute clinicians, though Sim Wallace placed too much emphasis on function in relation to form, while Alfred Rogers put an undue emphasis on exercises, as a method of correction of malocclusion.

One of the classics of English orthodontic literature is the *original* publication of Brash's Dental Board Lectures in 1929 and the chapter on soft tissues contains many statements which have withstood the test of time.

Present views can be summarized as follows:

(1) The basic structure of the jaws develops according to a predetermined pattern. However, the potential for growth cannot be determined at any particular time. Function, for example early feeding methods or the consistency of diet masticated, has no effect on the basic growth of the jaws.

(2) The teeth with their alveolar process develop between the influence of the cheeks, lips and the tongue. The relationship of upper and lower dental arches is determined by the size and relative positions of the basal elements of the jaws and reflect the shape, the resting position and activity of the soft tissues.

A rough classification of clinical types can be made, embracing skeletal, dental and soft tissue morphology (Gwynne-Evans and Tulley, 1955). Morphology of the soft tissues may be as inherent as the basic bony structures but there is a controversy concerning the abnormal activity of the muscles.

Rix (1946) focused attention upon the importance of the activities of the tongue and lips, with particular reference to swallowing. He described the atypical teeth-apart swallow in which the tongue did not mould the developing dental arches centrifugally. In 1953 he described many variations on this theme. Rix believes that in some instances a combination of change of tooth position and maturation of behaviour produces a change which is stable. Ballard believes that these patterns of activity are to a large extent endogenous. Gwynne-Evans has pointed out that the circumoral muscles, occupying a developmental position between the somatic muscles moving the limbs and the visceral muscles of the gut, are not so easily controlled by changes in tooth position or by exercises.

The American view is that many of these abnormal activities are habits developed either primarily, or that they are secondary to the dental alignment and they modify with treatment and exercise.

(3) Upper respiratory infections and obstructions, although they often accompany malocclusions, cannot be shown to be the direct cause but only an associated factor. The narrow maxilla is inherited and not due to lack of aeration of the antra. Naturally narrow nasal passages are more easily obstructed, although it is possible to find this facial type without any history of upper respiratory troubles (Fig. 6A).

The constriction of the dental arches on already narrow bases is due to the accompanying pattern of soft tissue morphology and function. There may be a low rest position of the tongue but the lack of lip seal is not necessarily an indication of mouth breathing. The tongue and soft palate form a posterior seal. Lack of lip seal in these cases may be due to anatomically short upper lip, or to separation of lips by the teeth, or to lips which have an innate posture which Ballard calls the incompetent lip posture. All three of these factors may be present.

(4) *Rest position.* The posture of the mandible at rest is a so-called constant for the individual (Thompson, 1946). In the infant the gum pads are widely separated at rest but as the teeth and alveolus develop the inter-occlusal clearance diminishes to 2–3 mm. in the molar region. The normal path of closure from rest to occlusion is a simple hinge movement.

Abnormal alignment of one or more teeth may act as a displacing factor to the normal path of closure. Grewcock and Ballard (1954) and others have described true overclosure in postural Class III and some Class II Division 2 malocclusions. This comes about by premature contact of teeth and sensory impulses from the supporting tissues of these teeth initiate a reflex avoiding pattern. The mandibular elevators carry the mandible past the normal centric position. Possibly the abnormal contraction of these muscles restricts the occlusal development of the cheek teeth.

Lateral displacement is also found initiated by abnormal tooth contacts. There is no overclosure in these cases and the correct path of closure is restored by grinding or repositioning of the teeth. In certain instances if the basic shape and behaviour of the circumoral and lingual musculature is responsible for the positioning of the teeth on the basal bones they must indirectly affect the path of closure. Therefore they influence the masticatory pattern, and if this argument is taken to its logical conclusion they might indirectly be concerned in temporomandibular joint disorders.

There are acquired postures of the mandible which are not the true rest position. These may be developed in Class II cases to overcome the inability to seal the lips and mask the retrusive appearance. Brodie calls this the "Sunday face". This is a position of rest established by habit. Some workers have described distal displacement and overclosure in a large number of Class II cases. They have not taken into account this acquired forward postural position and the return to true centric on closure.

Other Research Methods

Animal experimentation has, in the main, been disappointing and misleading. There have been many experiments where there has been surgical or other interference with muscle

function but in nearly every case there has been the problem of scar tissue or lack of proper control.

Observations from pathological conditions affecting muscle function in man may also be misleading but they do illustrate the malleability of the alveolar process. They tend, however, to give a wrong impression concerning changes in basic jaw structure. In the older textbooks, cases of bilateral ankylosis of the temporomandibular joint were often quoted in support of the hypothesis that normal masticatory function was necessary for good jaw development. We now know that it is the growth centre of the condyle that is affected in such instances, preventing mandibular growth.

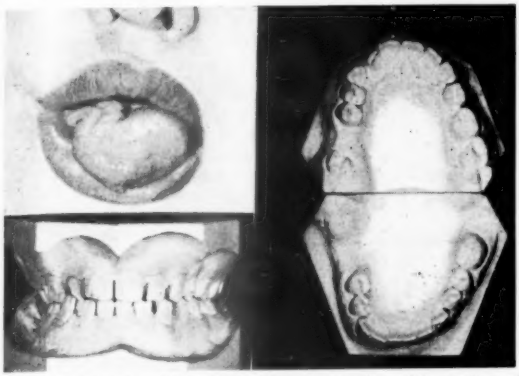


FIG. 1.—A case of right-side VII nerve palsy with section of hypoglossal nerve showing the effect of unilateral tongue paresis on the dental arch.

In cases of unilateral VII nerve palsy which have occurred at an early age during the development of the dentition there is no marked asymmetry of the dental arches, suggesting that the cheeks are not such important factors as the tongue at rest and in function in moulding the dental arches. However, Fig. 1 shows one case of VII nerve palsy where the tongue had also been affected by section of the hypoglossal nerve in an attempted transplant. This case shows a marked asymmetry of the alveolar process on the side with the abnormal tongue position and function. More teeth have been lost on the side where the normal cleansing action of cheeks and tongue was deficient.

In visiting a home for children with various upper motor neurone lesions it was interesting to note how few malocclusions there were among those children with unco-ordinated athetoid movements of the facial and lingual muscles but those with true spasticity of the tongue showed the dominant role of the resting position of this organ.

Cine fluoroscopy. The possibilities of studying soft tissues of the mouth with cine fluoroscopy are improving with the advent of electronic image intensification. A number of studies have already been made, notably those of Ardran and Kemp (1951). Other films of temporomandibular joint and nasopharyngeal closure in cleft palate cases have been made in the U.S.A.

Electromyography. This was first used to investigate dental problems by Moyers at the University of Iowa in 1949. The electromyograph amplifies and records the electrical potentials which develop when a muscle contracts. Much work has already been carried out on the electromyographic study of normal activity and on the type and siting of electrodes.

Moyers, recording from the suprahyoid group, especially the digastrics, has cleared up some of the controversy concerning the role of these muscles in opening the mouth (Last, 1954).

In studying specific functions the electromyograph is able to make progress beyond the purely visual and palpation methods of studying muscular activities.

Eschler in Freiburg has studied the masseteric activities of infants during breast and bottle feeding. His findings show, as one would expect, greater masseteric activity in breast-fed children and even if they had to go on to a bottle at an early age; those that were commenced on the breast continued to show greater suckling activity.

Many workers have been interested in masticatory activity and recordings from cases of normal occlusion agree that the masseter is the power muscle of mastication and the temporal the initiator of the movement and capable of more rapid but less sustained response. They have also shown the muscles of the balancing side may be as active in normal occlusion cases as on the chewing side. In the incision of food the masseter shows activity whereas the temporal, acting at a mechanical disadvantage, comes into play after the initial contact. In studying mastication it is important to obtain a natural setting for the experiment so that the patient does not chew according to a set pattern. The following observations can be made from my experiments which agree with the findings of other workers (Figs. 2 and 3).

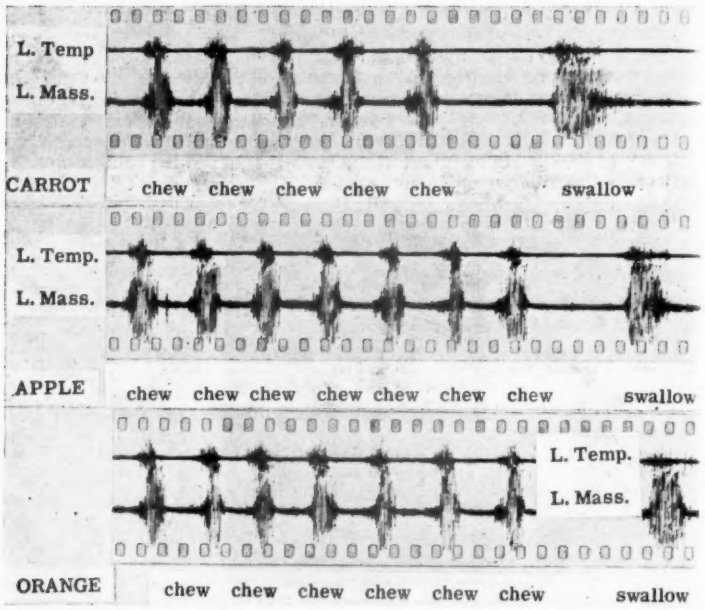


FIG. 2.—Examples of chewing and swallowing behaviour recording from temporal and masseter on a two-channel electromyograph. Note the rhythm, the sequence of contraction.

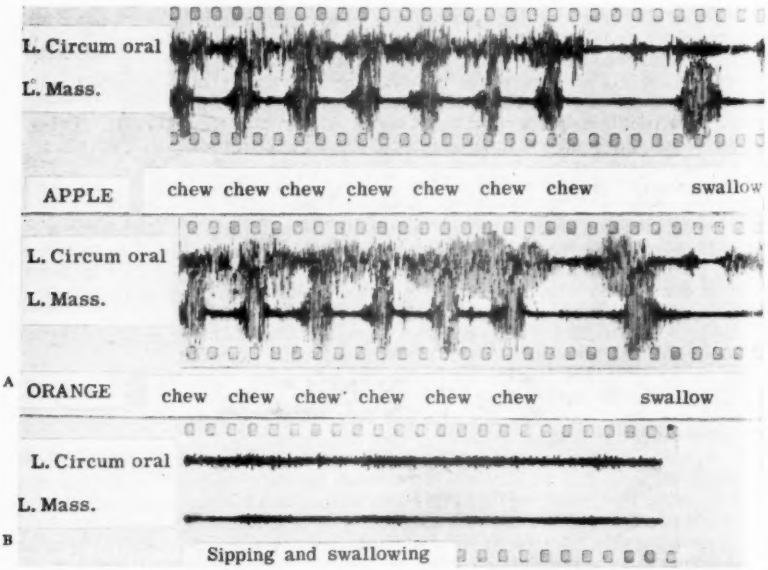


FIG. 3.—A, Examples of chewing and swallowing behaviour recording from circumoral and masseter. Note increased lip activity with succulent material and, B, the minimal activity of masseter during sipping and swallowing.

(1) The uniformity of the masticatory stroke from both masseter and temporal.

(2) The rhythmic activity of cheeks and lips between each masticatory stroke. (The recording from the lip muscles shows a finer pattern with a greater frequency indicating fewer muscle fibres controlled by one nerve fibre.)

(3) There is a wider band of masseteric activity with the same amplitude indicating a totally greater force in chewing the harder foodstuffs.

(4) When recording from temporal and masseter, the temporal contracts slightly in advance of the masseter reaching its peak potentials before the masseter.

(5) There is a definite relationship between amplitude, frequency of contraction and the size and toughness of the material.

(6) Even with normal occlusion there is often a habit or preferred side which is used mainly in chewing. This may have been initiated by some painful tooth or some local stimulus but Eschler has shown this development of a preferred side from early age in the weaned infant.

(7) When chewing on the preferred side the balancing side does not necessarily show as great a contraction of the masseter. However, when chewing on the unusual side the balancing side shows a contraction equal to the muscle on the chewing side.

Coincidently with the investigations of chewing, observations have been made concerning the state of the muscles at rest but there is controversy over the recordings from resting muscles. There would appear to be electrical silence even to the most sensitive apparatus, but at this high amplication, the problems of amplifier "noise" are very difficult. Using a loud speaker as Perry does it is possible to get "audio silence". I have made similar investigations with the lip muscles. Here more than in the masseter and temporal, relaxation is difficult to obtain but there is virtually electrical silence.

My main interest in the use of the electromyograph started with an investigation of normal swallowing activity as described by Whillis and Rix. This was achieved by placing electrodes as is illustrated in Figs. 4 and 5. The electrodes on the masseter were placed along the main course of the muscle, the upper, 1½ in. from the outer canthus of the eye, and the lower, 1 in. from the angle of the mandible.

The electrodes on the lips were placed one on the upper and one on the lower just medial to the corner of the mouth recording the general activity of the orbicular sphincter. Recordings were taken from both sides.

At the moment of swallowing when the mylohyoid muscle contracts there is normally a firm contact of the teeth achieved by masseteric contraction and the amount of lip activity is minimal. The teeth act as a rigid walled barrier to the tongue which is contained within them. Rix has emphasized this as being an important factor in the moulding of the dental

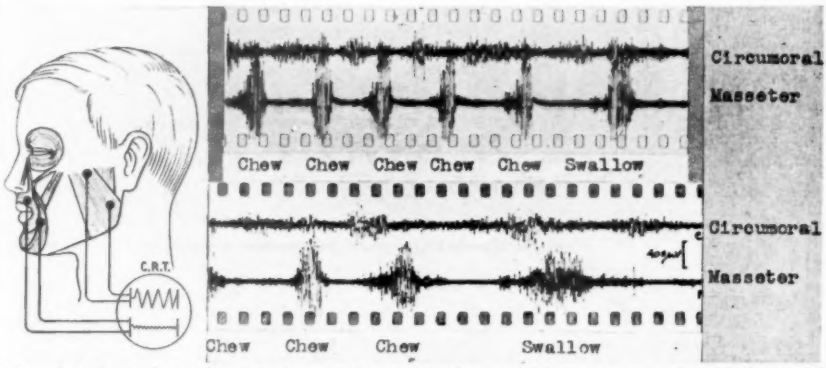


FIG. 4.—Electrode positioning in studying swallowing activities with examples of "normal" (teeth together swallow) after chewing. (From Tulley, W. J. (1956) *Amer. J. Orthodont.*, **42**, 801, by kind permission.)

a ches. In studying examples of chewing followed by swallowing in cases of normal c clusion the following observations can be made (Fig. 4):

(1) In chewing and swallowing of a hard biscuit the masseteric contraction at the moment c swallowing equals that of each masticatory stroke.

(2) The lip activity is minimal in swallowing.

(3) The lip activity is increased in the chewing and swallowing of succulent material such as a piece of orange. The masseter may or may not contract as strongly as this.

(4) In sipping and swallowing liquid from a cup the tongue acts as a conveyor belt and there is little activity from the masseter.

Studies of Malocclusion

Studies on cases of malocclusion allow the following general observations to be made.

Moyers and others have shown an increased activity of the posterior retracting fibres of the temporalis in cases of Class II Division 1 closing from rest to occlusion. They tend to infer that this is an ætiological factor in some types of mandibular retrusion. It has already been stated that many of these cases adopt a forward resting posture to effect a lip seal and these potentials may be recorded from the posterior temporal producing retraction on closure.

Greenfield and Wyke (1956) have also shown this increased activity of the posterior fibres of the temporalis on one side in cases of unilateral displacement of the mandible, as reported by Grewcock and Ballard (1954).

Zwemer (1955) has shown that in a normal subject closing from rest position to occlusion there is no appreciable activity of the masseter and temporalis until tooth contact is reached. In comparing these cases with cleft palates where there is a defect in vertical development of the alveolar process he shows an excessive contraction of the masseter and temporal muscles to reach occlusion. This activity disappears if the excessive inter-occlusal space is diminished by overlays. This supports Ballard's views of the abnormal contraction of the mandibular elevators in postural Class III cases where there is overclosure and in some cases of Class II Division 2 type where there is distal displacement. Ballard points out that the normal relaxation of the closing muscles does not occur following arrival at the level of true centric. This is significant when considering the vertical development of the cheek teeth.

In studies of chewing in cases of malocclusion many authors have shown that there is not the same clear-cut pattern of masseteric and temporal activity. Perry calls it a searching pattern. Pruzansky demonstrates the chopping pattern adopted by patients with adverse cuspal locking. I do not believe, however, that we are anywhere near identifying the particular type of malocclusion from an electromyograph of the chewing activity.

In this study of abnormal swallowing I have been able to apply the work of Rix and show the increased activity of the circumoral muscles in certain cases when the mandible is not fixed to the maxilla by a strong masseteric contraction (Fig. 5). The electromyograph,

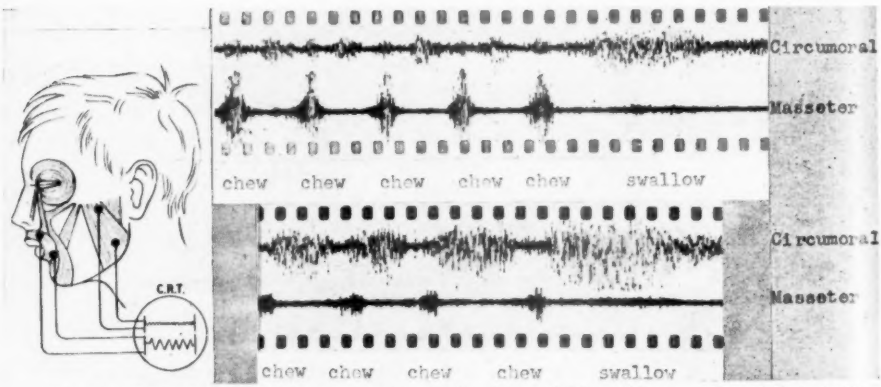


FIG. 5.—Electrode positioning in studying swallowing activities with examples of "atypical" teeth apart swallow after chewing with excessive circumoral activity. (From Tulley, W. J. (1956) *Amer. J. Orthodont.*, **42**, 801, by kind permission.)

however, cannot distinguish the subtle differences in activity of lips and tongue described by Rix (1953).

It has previously been stated that the activity of the circumoral musculature may dictate the position of the teeth which in turn may dictate the masticatory pattern. The deciduous incisors, however, being smaller and not projecting far into the oral cavity are not subjected to adverse muscle forces to the same extent as are the permanent teeth.

Mr. R. E. Rix has allowed me to report a case where there was a normal deciduous dentition

but with the advent of some permanent teeth adverse circumoral forces have influenced the developing permanent dentition to mould an upper arch which is too narrow to receive the mandibular dental arches in true centric. There has been therefore a mandibular displacement in the path of closure to the patient's left. This is an excellent example of a clinical problem and the electromyogram shows the excessive circumoral activity and the type of swallowing behaviour. It also emphasizes the practical point that many malocclusions are not so commonly manifest in the deciduous dentition and even when they are, orthodontic treatment at this age is virtually a complete waste of time.

In cases of acquired postural positions of the mandible some ill-defined electrical activity can be detected in the mandibular elevators. In recent papers Perry and Jarabak and others have shown that where there is the vicious circle of abnormal tooth position, temporomandibular joint disorders and abnormal muscle function, muscle spasm in producing cervical facial pain can be diagnosed by the electromyograph. I feel that we shall hear a lot more about this in the near future. Campbell (1954) forecast the use of this apparatus in studying some types of facial pain.

Ballard, in describing what he calls the incompetent lip posture and morphology, has shown that many patients with lack of lip seal have lips that are anatomically long enough to affect a seal but have a poor posture. He has described how these individuals have to make a conscious effort to seal their lips by contracting the orbicular sphincter and although it may become an almost unconscious habit, it is never permanent. This abnormal activity of the lower lip is one of the factors controlling the position of lower incisors. Ballard has pointed out the electromyographic signs and Fig. 6 B, C is an example.



FIG. 6.—Patient at 8 years and 15 years illustrating: A, the so-called "adenoid facies" without any upper respiratory obstruction, the poor posture of the lips. B, seven years later without any treatment, conscious effort to affect lip seal. C, Electromyogram showing activity of lips in order to maintain lip seal.

Finally, I do not believe that electromyography has any future directly related to clinical dentistry as some writers have suggested but I feel it has a definite place in future research by dental clinicians.

CONCLUSIONS

Experimental results so far seem to indicate little change in treatment from that already adopted as a result of clinical observation.

The answer to many of these changes lies in the fulfilment of the growth potential not only of the skeleton, but of the soft tissues also, and in the maturation of the facial musculature which takes on the "adult" mask. With the increasing worries of raising a family and of income tax, we do not expect to see the same lax lip positions of childhood. With the desire of the young lady to appear attractive, we do not see the same "deadpan" face of the preadolescent (Fig. 6 A, B).

These age changes help the orthodontist but create a new problem. Because the neuromuscular system is affected by emotional states some cases of facial pain may be due to spasm in the masticatory muscles. There would appear to be a need for further work upon the physiology and maturation of normal and abnormal orofacial muscular behaviour.

ACKNOWLEDGMENTS

My thanks are due to Mr. R. E. Rix and Mr. K. E. Pringle for allowing me to show cases of patients under their care at Guy's Hospital Dental School. To my colleagues in the Physics Department who have developed the Electromyograph for my use. To Miss Whiteley of the Dental Photographic Department and Mrs. Rawlins for the illustrations.

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Section of Psychiatry

President—WILLIAM SARGANT, M.A., F.R.C.P., D.P.M.

[*February* 12, 1957]

DISCUSSION: THE PSYCHIATRIC INDICATIONS FOR THE TERMINATION OF PREGNANCY

Dr. J. D. W. Pearce:

In the United Kingdom abortion is lawful only if done in good faith for the purpose of preserving the life of the mother. In this context life includes health, and abortion is lawful only if other effective treatment does not exist, and if the probable consequence of the continuance of the pregnancy will be to make the woman a physical or mental wreck, whether such a result is likely to be permanent or not. Abortion "to protect the health of the unborn child" is always a felony. In Sweden the 1946 Abortion Act enables abortion to be done lawfully on medical, medico-social, socio-medical, humanitarian and eugenic grounds.

The two essential psychiatric questions to be answered are:

(1) What severe psychiatric disorders are precipitated or seriously aggravated by pregnancy or childbearing, and what is their subsequent history?

(2) Which, if any, of these conditions is abortion likely to relieve or cure? The adverse effects of abortion must also be examined.

Most textbooks say little or nothing relevant. Lewis (1950) says that "the termination of pregnancy is called for on account of the mental condition when there are symptoms of organic psychosis which are likely to get worse, a history of suicidal attempts or infanticide in connexion with previous pregnancies and a depression in this one, or if on other grounds there is a clear risk of suicide or other untoward result of the mental illness, should pregnancy continue—The question must turn mainly on the therapeutic value of terminating the pregnancy".

Tredgold and Tredgold (1953) say: "Mental disorder which appears in the first half of pregnancy, and before the child is viable, usually passes when quickening takes place, whilst disorder arising after quickening usually persists for some time after birth and is unaffected by abortion."

Hart (1929) summed up the indications and contra-indications for therapeutic abortion: for pre-existing psychosis, terminate only very rarely; for schizophrenia arising in pregnancy and for recurrent psychosis not related to former pregnancy, no termination; for recurrent psychosis of pregnancy and puerperium, terminate; for severe reactive anxiety and depression stemming from the pregnancy, termination depends on a question of degree.

In 1931, the Sections of Obstetrics and Gynæcology, Medicine and Psychiatry discussed the medical indications for abortion. James (1931) said that where loss of sleep, of weight, and of insight were persistent and accompanied by mental symptoms, abortion should be considered without too much waiting and seeing.

With modern effective treatment one would expect the indications now to be far fewer, but fully developed psychiatric out-patient services have brought more patients under psychiatric enquiry.

The post-war literature shows but little general agreement on the indications for and the therapeutic effectiveness of abortion. Hobson's (1953) main criterion is the risk of suicide, especially in severe reactive anxieties and depressions. Mental deficiency, psychopathic personality and established mental illness are not, in themselves, indications.

Eastwood and Heuser (1947) think that very few, if any, psychiatrists would abort in any of the psychoneurotic reaction types; in only a few recurrent schizophrenic and manic-depressive psychotics owing to inability to care for the child (and similar social criteria inadmissible here); but in single, young women with resultant self-guilt and self-depreciation, plus strong suicidal drives, each case is to be considered on its own merits. This is a narrow field as it includes only those with fully inturned aggressiveness, not those who slash around with threat of self-destruction.

Kummer (1953) sees pregnancy and parturition as no more than precipitating stresses and not basic causes of associated mental disorders. Important factors are the pattern of previous psychotic reactions (severity, duration, reversibility, relation to pregnancy), the physical constitution of the patient, the religious and other personal beliefs of the patient and her family, the desire for parenthood, and the number of living children. Donnelly (1955), however, dismisses all economic and social criteria.

Kraepelin (1909) observed that abortion was more often a precipitant than an alleviant of mental disease. Ekblad (1955) in his Swedish monograph found that the greater the psychiatric indications for legal abortion, the greater the risk of unfavourable psychic sequelæ.

I wrote to some forty-five psychiatrists and to one general practitioner, in the hope of finding some general measure of agreement on the criteria on which decisions to abort are based, and found this largely lacking.

Many approach the problem by asking three questions:

Is this woman's mental state due to pregnancy?

Will abortion relieve the mental illness?

If so, should she be sterilized?

The answers to such questions are mainly subjectively based. There is relatively little firm knowledge of the course of psychiatric illness in pregnancy and the effects, good or bad, of abortion.

Here are some dogmatic statements from some of my correspondents:

(1) Termination has never had a beneficial effect in any case.
(2) The only criterion is severe, chronic, unremitting schizophrenia worsened by pregnancy.
(3) The only criterion is schizophrenia with a bad family history.
(4) Terminate only in some cases of previous puerperal psychosis and mental deficiency.
(5) Each case is considered on its own relative merits, there being no hard and fast rules.

Four or five of my correspondents accept both of the following criteria:

(1) A clear causal connexion with the pregnancy plus the severity of the illness.
(2) A previous similar illness in childbearing.

Two more accept the first but reject the second whereas yet three more accept the second while rejecting the first.

There is much more agreement about *not* aborting than about aborting. Many do not refer to *schizophrenia* at all and presumably never advise abortion: some say they never abort, but a few do so, e.g. in most cases; or if coupled with a bad family history; or if pregnancy is causing psychological strain; or if it is of the covert type keeping out of hospital. With *depressions*, the great majority do not terminate. Almost all regard the threat of suicide as no indication. Many do not refer to low-grade *mental deficiency*, but one invariably aborts and another sometimes. Most do not refer to *neurotic reactions*, some categorically say they never abort, only a very few do so. In *psychopathic states* one or two will abort if in a state of near-psychotic excitement: the rest never.

Two or three add up the various minor factors, but Donnelly (1955) says "One should have one good reason for doing a therapeutic abortion. Three or four minor ones do not add up to one good one".

Some unusual criteria are advocated by a very few of my correspondents, but the law would not permit the adoption of some of these.

The general practitioner says: The general practitioner can help the psychiatrist because he knows the patient's background and personality. Those who become really psychotic or attempt suicide are candidates for abortion, but this may not clear up the trouble. Such cases are not nearly as common as the woman who is just fed-up because of an unwanted pregnancy. The general practitioner can coax most through the first trimester when the desire to be rid of the baby usually subsides. The distressed women, not obviously psychotic, but with threats of suicide difficult to assess are for the psychiatrist. He would never recommend abortion without a psychiatric opinion, and assumes that the consultant would want the general practitioner's full backing.

Most agree on the need to admit patients to hospital for full study and to collect the facts before reaching a diagnosis. One correspondent says "sheer diagnosis is not enough. The decision to abort or not may rest on other circumstances, e.g. husband, home, chance of adequate psychological help". And most agree that most patients can be safely brought through to full time with adequate medical, nursing and social aid.

The criteria most of us use are based on a tacit assumption that abortion *per se* has a therapeutic effect in a wide but undefined range of psychiatric maladies, and but few of any bad effects. But we need more knowledge about the natural history of psychiatric illness associated with pregnancy, and the late results of abortion, and more studies to provide valid criteria.

Until such time I would advise some curtailment of so much clinical freedom to recommend abortion. There should always be at least two independent psychiatric assessments, and in-patient examination has much to commend it. In Colorado (Ebaugh and Heuser, 1947) since 1937 an abortion committee, which includes the professors of medicine, obstetrics and gynæcology, and psychiatry, decide on each case after full in-patient study: surely an excellent plan.

The regular general practitioner must always be in the picture. I feel insecure about any patient coming from a general practitioner who has seen her for the first time because of her predicament.

Casper (1934) said that scientific men should apply themselves more diligently to the task of saving both mother and child. All our resources—medical, psychiatric and social—should be used to tide a woman over, if needs be as a voluntary in-patient, until quickening, as so many mothers then settle down. Moreover, hysterotomy enables her to be sterilized at the same time if indicated.

I tend to follow Hart's criteria, but I sometimes have misgivings over my rather legalistic attitude. Religion is above medicine, and religious differences are to be accepted, and respected. None the less ethical, moral and social issues inevitably complicate our thinking about this subject. History shows the transient nature of social and eugenic criteria. Ebaugh and Heuser (1947) say that morally the medical profession cannot condone abortion for economic or sociological reasons, but one cannot but wonder what effect it might have on juvenile delinquency, alcoholism, mental deficiency, suicides, homicides, arrests, &c.

Some psychiatrists advocate eugenic abortion. A case may, in principle, be made out for this, but it could be applied only where there were most reliable criteria. It is difficult, indeed impossible, to remain entirely a medical man in considering such a problem. Twenty-six years ago the whole emphasis seems to have been on mental disorder. Now we have the concept of mental health, and a further evolution in our thinking on these matters is under way.

Just before Bourne's trial at the Old Bailey, James (1938) wrote: "It should not be beyond the ability of two learned professions to devise a formula which acknowledges 'reason' to be as important as 'life', and which gives legal sanction to practitioners and experts alike to consider the 'health' of the mother in a very wide sense." It may be that the time is ripe for a critical restatement of such a formula.

What are the subtle archaic motives which make some of us feel so uneasy about assuaging a woman's distress by a fully warranted therapeutic abortion, as if we were doing something against our conscience?

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Professor E. W. Anderson:

Study of the literature over the past thirty years shows little general agreement over the psychiatric indications for termination of pregnancy. At one extreme, some, like Bumke, believe that such indications hardly exist, at the other those like Brill would extend them widely. The majority occupy a midway position. In general medicine the indications are tangible and on the whole widely accepted. In psychiatry this is not so. The criteria of psychiatric diagnosis vary with the individual observer, notably with the diagnosis of schizophrenia. Since many writers hold that pregnancy acts adversely on the schizophrenic process diagnosis is no mere academic matter. As atypical psychoses with prominent schizophrenic features, some of them benign, others not, are frequent amongst puerperal illnesses a history of such in a previous confinement might lead to difficulty in deciding action, if the view just mentioned is accepted. Perhaps the most important factor hindering basic knowledge of the problem is the paucity of clinical material and the extreme difficulty of investigating what exists in a scientifically valid way.

Numbers of all therapeutic abortions to live births in seven leading American clinics

ranged from 1 : 35 to 1 : 16,750. In the latter series none for psychiatric reasons (Cosgrove and Carter);

84 : 25,516 (female hospital admissions over ten-year period) 6 for psychiatric reasons (7%) (Dannreuther);

1 : 500 (deliveries), 80 therapeutic abortions in twenty-year period, 1 psychiatric (1·25%) (Siegel and Kohn);

280 : 46,841 pregnant women treated over ten-year period, 9 psychiatric (3·2%) (Kuder and Finn);

Of 1,489 therapeutic abortions over ten-year period, 8 on psychiatric grounds (0·54%) (Heidler);

15 : 5,000, none psychiatric (McIlroy);

51 : 569 women referred for opinion on termination, 4 psychiatric (Gornick);

593 : 44,003 deliveries, 74 psychiatric fourteen-year period (12·5%) (St. Mary's Hospital, Manchester);

28 : 2,665 abortions, none psychiatric (Davis).

No doubt, as Fairbairn remarked, there is a big difference between the figures for private and hospital practice.

In England abortion is a felony, although the law, not as clear on this matter as it might be, tolerates it for valid medical reasons. The other indications, the social, the humanitarian and the eugenic are not recognized. A further factor hindering progress would seem to be the frequent failure to separate the medical from the social indication which in psychiatric cases is persistently obtrusive and often so closely interwoven with ætiological considerations, that its sharp divorce from the medical becomes virtually impossible. This has been widely recognized, e.g. Maier and Hart. It is not surprising therefore that data are still fragmentary and contradictory. The remarkable thing is that comparatively little has been done to study the problem systematically. Historically the literature falls into two periods, that of impressions and that of attempted systematic study. English opinion as expressed by the Royal Medico-Psychological Association in 1927 (Lord) was, on the whole, against abortion on psychiatric grounds and Robinson in 1933 elicited a similar view from 95 English psychiatrists. Hart, however, whilst doubting its value in psychoses advised greater flexibility of approach to the matter in the psychoneuroses. Kogerer (1931) referred to observations by several authors that certain schizophrenics became worse with pregnancy, but this was certainly not invariable. Boyd (1942) summed up the matter by admitting the lack of basic knowledge and hence the entire unpredictability of results of therapeutic abortion in psychiatric cases. The second period was inaugurated in Switzerland following a change in the Swiss Federal law by which abortion became permissible where continuation of pregnancy seemed likely to damage the mother's health. Only four cantons had previously recognized this. A series of important studies appeared by Binder and a number of others including Zolliker (1937–38), Glaus (1948), Maier (1932) and Schneider (1942). Binder from his series of 350 unmarried mothers sought to establish more precise psychiatric indications. He found that 7% of these women developed chronic psychiatric invalidism. He postulated two essential criteria: (1) a pre-existent abnormal psychic constitution, and (2) a degree of situational stress incapable of relief by the normal social measures. None of his normal women developed lasting mental illness whatever the stress. Interruption is not called for in every schizophrenic but only where symptoms appear for the first time at the beginning of a pregnancy or where already existent process symptoms become worse or a previous pregnancy seemed to have precipitated the illness. More recently Ekblad in Sweden has published the results of legal abortion in 479 women. This study also became possible through legislative change. 65% of these women withstood the procedure without ill-effects, but some 25% showed guilt reactions varying in severity. Siegfried found 36 such (59% in a series of 61. Polonio and Figueiredo found abortion responsible for 20% of the attacks in a series of 244 cases of puerperal psychosis. This is at variance with Vallejo Nagera's (1945) figure of less than 2% for both spontaneous and induced abortion. Polonio believes that pregnancy, far from being traumatic, actually protects against mental illness.

In the Manchester University Department of Psychiatry a study of this problem was begun in 1950. The following preliminary and provisional findings relate to 52 women, 49 pregnant and 3 not pregnant, referred for opinion on sterilization. I interviewed each patient personally, a history was obtained from the nearest relative by a psychiatric social worker and a follow-up attempted. This ranges from six months to five years. In addition each patient was given a so-called projective test by a psychologist. The women were mostly out-patients, although 9 were admitted for a time before and/or after confinement. Admission of each case, although ideal, was impracticable for various reasons. The average age of the group was 29·7 years (range 20 to 43). 5 were single, 2 widowed, 45 married. The majority, 29, were Anglican, there were 9 Roman Catholics and the remainder of other persuasions. The number of pregnancies ranged from 1 to 8. 39% were in their first or

second, and 43% in their third or fourth. The largest number (14) were in their third, 10 in their first, and 1 in her eighth pregnancy. 17 were recommended for termination, in 12 this was done. Sterilization was performed simultaneously in 5 of these. 6 pregnant women were recommended for sterilization only, which was carried out in 3. Of the 3 non-pregnant sterilization was advised and performed in 2.

Diagnostic categories comprised chiefly three groups totalling 40 patients, personality disorder 13, affective states 17 and asymptomatic 10 (including 3 women with a history of previous puerperal psychosis).

The remainder were made up as follows: Obsessional states 7; hysterical reactions 2; epilepsy with psychiatric features 2; disseminated sclerosis with psychic changes 1, and one other with disseminated sclerosis included in another category. 4 patients were considered too late for termination, although in 3 this would have been advised had they been seen earlier. 10, possibly 11, of the pregnancies were illegitimate (*c.* 22·5%). Some degree of suicidal risk, occasionally serious, existed in 23. This is at variance with Binder's findings and also with our own elsewhere in a study of young unmarried mothers. 10 attempted abortion, 1 other considered it and alleged spontaneous abortion occurred in 6 (*c.* 12%).

This compares with 29% in a similar series (Neuweiler), 17% and 17·5% respectively in two similar, larger series (Rumpf and Noell, 1950; Amstad 1934). Only the first 42 cases are considered here, the remainder have been under review for too short a time for adequate follow-up. Of the 42, in 9 follow-up was impossible. Follow-up is more than usually difficult with these women, the mentally normal when referred often leave in anger and refuse further access, many are unusually feckless and shiftless and tend, more than average patients, to drift away. Of the 11 under review whose pregnancies were terminated only one benefited conspicuously, a widow of 39 raped by a stranger. She reacted with shame and grief, could not face her adolescent children and attempted suicide. Since the latter was virtually certain if her pregnancy continued and since neither admission nor social measures would have helped, abortion was advised. In 10 others the benefits were more doubtful. In one who had had a previous, possibly schizophrenic, puerperal illness, termination may have prevented an exacerbation. 2 others showed some symptomatic improvement. In 6 no benefit was noted, while in the last 2 no further information was obtainable. Of the 5 recommended for termination, one who refused it still had symptoms of a previous puerperal illness when first seen. She went to term without mishap and two years later was well. One other, a sensitive anankast, developed a puerperal illness diagnosed elsewhere as schizophrenia and on follow-up was still sensitive and suspicious. Of the remaining 3 there is no information. Of the 32 not recommended for termination 24 are considered here. 5 attempted abortion, 1 considered it and 3 had an alleged spontaneous abortion. 12 went to term without lasting ill-effects. 6 showed little or no improvement. It is possible that termination might have helped 3 of them. In 6 follow-up was impossible.

Obviously no firm conclusions can be drawn from such a small series. In some cases of schizophrenia abortion may be advisable. There were no certain schizophrenics in this series, hence on the basis of this material I can make no personal judgment. Where suicidal risk is real the patient should be admitted. By this means several of my patients have been brought successfully to term. Sterilization was followed by striking improvement in one woman, in another associated also with termination, the opposite. In the light of this study I would strongly advise against termination or sterilization in women with strong anankastic and depressive features since either is likely to be followed by severe self-reproach, of which 4 instances were found in this series. Severe economic and marital stress existed for 12 women. I believe we tend to underestimate considerably the capacity of woman to withstand stress. Nevertheless, if the State insists on a woman bearing her child, the State must ensure more adequate social services, in particular more trained social workers, than exist at present. I believe that thereby fewer therapeutic abortions on psychiatric grounds would be necessary. If I have gained one impression from this study, it is that abortion in the large majority of psychiatric cases has very little medical justification.

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Professor W. C. W. Nixon:

It would appear from the legal aspect that the onus is on the operator—the gynæcologist—to justify his action of termination of pregnancy. It is he who does the operation, not the psychiatrist. It is he who carries the full responsibility for acting in good faith. Good faith are the operative words. The general surgeon or the physician rarely has to carry a responsibility of such gravity. Who can blame my colleagues who shrink from exposing themselves to such an exacting test—moral cowardice is a question of degree? Yet there are women whose pregnancies should be terminated on justifiable grounds but in whom an abortion is not done because the gynæcologist is fearful of being dubbed an abortionist. This situation arises especially in small provincial, as distinct from teaching, hospitals.

The threat of suicide is one which I, as a gynæcologist, find difficult to assess but it is possible to under-estimate the gravity of this threat. If a patient does not gain relief from an interview with a gynæcologist or psychiatrist then she may do something drastic. If we still subscribe to the Hippocratic oath then it is the duty of doctors to prevent patients injuring themselves. If we are convinced an injury is going to happen then we must act. Suicide is a destructive act against society. Apart from the complete destruction of the individual there are varying degrees of injury, either physical or psychological. We must therefore, accept a broad connotation of health if society is to be protected from the loss of properly functioning individuals and if we are to prevent such persons becoming permanent invalids.

There are those who consider that the only valid indication for termination of pregnancy is when there is also an indication for sterilization. I think vindictiveness of this kind is a form of blackmail which should have no place in gynæcological practice.

I cannot deny that some psychiatrists have gained the reputation of being "abortion easy" and that patients are misled in the belief that termination can easily be obtained on psychiatric grounds. Perhaps it is for this reason that some gynæcologists resent being requested on psychiatric grounds to terminate pregnancy and, therefore, adopt an obdurate and contrary attitude. There is also the impression that we are being employed solely as mechanics. Yet I fail to see how any gynæcologist, unless he has made a special study of psychopathology, can question the opinion of a reputable psychologist. The operative word is "reputable". There are "consultoids" in every medical specialty and if I am to be used merely as a surgical technician then I will be directed only by those whose opinion I respect and who I know act in good faith.

In view of the stand that many gynæcologists take against the advice of psychiatrists—a stand which is essentially protective, it has been suggested that the way out of the impasse psychiatrist *v.* gynæcologist is the establishment of Abortion Panels. By such a system any imputation that abortions were done on flimsy indications could be countered. Such a panel was instituted ten years ago by Mr. Philip Mitchell, senior gynæcologist at the Royal Hampshire County Hospital at Winchester.

Just as a surgeon follows up all cases on which he has operated so should a psychiatrist continue to supervise the care of all women who have had a termination. If the psychiatric indication for this operation is made urgent then I see no reason why with the termination of pregnancy the psychiatrist should cease to be interested in the woman's future. Does the evacuation of the uterus cause an immediate amelioration of the psychosis? I venture to

suggest that psychiatric care should be an important part of the rehabilitation that a woman needs after this operation. We are all aware how some patients deeply regret this operation and develop a severe depression.

It is asking a lot of the gynæcologist to repeat the operation a year later and those who have the psychiatric responsibility for these patients must arrange for proper contraceptive advice or alternatively seriously consider the advisability of sterilization.

During the years 1938–1956 (inclusive) there were 509 cases of termination of pregnancy at University College Obstetric Hospital. Of these 198 (38·9%) were for psychiatric indications.

This is not the time to describe surgical techniques for termination of pregnancy. I prefer vaginal hysterotomy; it is possible to sterilize at the same time provided the gestation is not greater than twelve weeks. I find I am supported in this method by my colleagues in Sweden who have had far greater experience than I. The real problem is when the pregnancy is so advanced in the second trimester that an abdominal hysterotomy is necessary. This operation is really a Cæsarean section in miniature and the fœtus may survive apart from the mother. I do not think any gynæcologist should be asked to terminate at such a late stage and the onus should be placed fair and square on the psychiatrist to continue treatment of the patient in an institution.

Of all gynæcological operations that of therapeutic abortion is the one that causes me most discomfort. Not only is there the destruction of the fœtus—one can feel the shudder of the theatre staff—but also the inherent risk of uncontrollable hæmorrhage. There is the constant vision of the coroner's court—deaths do occur.

The *immediate* operative risks are those of hæmorrhage, perforation or sepsis, the *remote* are sterility and habitual abortion due to laceration of the cervix. Perhaps the sudden evacuation of the uterus may lead to "endocrine shock" which may later influence menstruation (dysmenorrhœa, menorrhagia), ovulation, or even the personality of the individual.

Mr. Aleck Bourne said that abortion is useless for treatment of an established psychosis complicated by pregnancy. After the third month vaginal abortion becomes an increasingly dangerous operation as time passes, and, when performed for a mental condition short of psychosis, is often followed by remorse which will aggravate the patient's neurosis, perhaps for years.

Abortion for any mental illness is seldom necessary, for the majority of patients become reconciled to the prospect of having a baby, after the middle of pregnancy. Suicide is often insincerely threatened as a kind of blackmail, but if, in the opinion of a psychiatrist, suicide is a genuine danger pregnancy should be terminated. As abortion cannot be repeated, and as contraception is unreliable in the hands of many of these patients, it is occasionally necessary, where the mental condition is regarded as permanent during the childbearing period, to sterilize at the time of hysterotomy.

Dr. Eustace Chesser:

It seems that the psychiatrists are not familiar with the usual psychological factors justifying termination of pregnancy. Greater reliance should be given to the general practitioner's opinion with his unique knowledge of the patient and her background.

Mr. Aleck Bourne suggests that sterilization should always accompany termination; why? To say "you should not have a child" is a far cry from "you cannot have a child". The mentally-sick patient of to-day may well be the mentally-healthy patient of to-morrow.

Dr. Noel G. Harris:

Occasionally a request is made to terminate a pregnancy not for the sake of the mother, but for the sake of the father. A recent example of that was seen with a woman married to a man who had had psychiatric treatment and was thought to be not far off a schizophrenic breakdown when her first pregnancy began. The father was distressed at the idea of the added responsibility of a child. His wife became anxious and distressed at the attitude her husband adopted in case it precipitated a complete breakdown in him. The psychiatrist who had treated the man thought the pregnancy should be terminated.

It is not uncommon to find that women who are sent up for termination of pregnancy have had no education or advice on birth control. Psychiatrists, obstetricians and general practitioners should see that married couples get adequate knowledge and instruction on this when they want it.

Dr. G. F. Abercrombie said that few general practitioners saw enough of these patients to form an opinion, but that he himself was becoming increasingly convinced that termination of pregnancy on psychiatric grounds was not the right answer.

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President—D. V. HUBBLE, M.D., F.R.C.P.

[*November* 23, 1956]

Congenital Agranulocytosis.—J. R. K. HENRY, M.B., D.C.H. (for J. P. M. TIZARD, M.R.C.P.).

Girl, aged 6 months. Admitted to hospital on 16.5.56 aged 16 days. She was the first baby, born at home after a normal pregnancy and delivery. Both parents were healthy.

Two days before admission there was a thin watery discharge from the left ear, and the day before admission she developed a profuse but clear nasal discharge, which interfered with her feeding. There were some small glands in the posterior triangles of the neck.

On the day before admission she had had two doses of 2·5 ml. of Cremotresamide (total of 0·2 gram sulphadiazine, 0·2 gram sulphacetamide and 0·1 gram sulphamerazine). Blood count on admission: Hb 16·3 grams%, W.B.C. 7,000/c.mm. Eosinophils 23% 1,610/c.mm. Lymphocytes 68% 4,760/c.mm. Monocytes 6% 420/c.mm. Türk cells 3% 210/c.mm.

A bone-marrow examination two days later showed erythropoiesis to be proceeding normally. Granulopoiesis was abnormal, the striking feature being the complete absence of neutrophil myelocytes, metamyelocytes and polymorphs, though eosinophils and basophils were present and developing normally. There was a slight excess of blasts. Megakaryocytes were present in normal numbers.

A nasal swab, throat swab and swab from the left ear grew *Staphylococcus pyogenes* which was sensitive to penicillin. Plasma proteins and electrophoretic pattern were normal.

She was treated with penicillin and made some improvement. Two weeks later she developed an abscess in the left cervical region, probably as a result of withdrawing blood from the external jugular vein. The organism cultured from these lesions was again a *Staphylococcus pyogenes* which was now resistant to penicillin.

She has had a further four admissions for septic skin lesions, tonsillitis and otitis media. Repeated examinations of her peripheral blood have shown a constant absence of neutrophils with a normal number of lymphocytes and a raised eosinophil count.

An interesting feature was that examination of her plasma proteins showed a gradual reversal of the A/G ratio, with a marked increase in the gamma globulin. The patient was given cystine 0·5 gram t.d.s. by mouth for two weeks with no alteration in the white cell count (*see* Kostmann, R. (1956) *Acta pædiat. Stockh.*, Suppl. 105).

Discussion.—If the very small dose of sulphonamides given on the day before admission can be ignored, it seems reasonable to consider this as a case of congenital agranulocytosis and similar to those described by Kostmann and considered by him to be inherited recessively.

It seems probable that this is a rare disease which, in the past, may have hidden under names such as pemphigus and cancrum oris, and has only come to light with the advent of antibiotics. These, although not altering the final prognosis, may prolong life for several years.

POSTSCRIPT.—The patient died on 17.1.57.

Obstructive Jaundice and Sepsis Following Exchange Transfusion for Group B Incompatibility.—LESLIE G. ANDREWS, M.B., D.C.H. (for J. P. M. TIZARD, M.R.C.P.).

Girl, aged 4 months. Born July 27, 1956. She became jaundiced within twenty-four hours of birth due to Group B incompatibility. She was severely affected and in all, three exchange transfusions were performed, through the umbilical vein. The serum bilirubin at its highest was 35·2 mg./100 ml., most of the pigment being of the indirect reacting type. No signs of kernicterus developed. Prophylactic antibiotic therapy was given following the second exchange transfusion.

Moderate jaundice persisted. On the 10th day of life the child became acutely ill, and had hepatosplenomegaly, veins coursing from the abdomen to the chest, ascites and some leg œdema. She was thought to have developed either a cholangitis or abscesses in the liver. The ascitic fluid grew *Staphylococcus pyogenes* resistant to the antibiotic used. At the same time the jaundice increased and the stools became pale. The serum bilirubin was now mainly of the direct reacting type of pigment, the child having developed an obstructive jaundice.

The infection gradually abated with a change in antibiotic therapy, but on the 52nd day of life she suddenly developed an acute intestinal obstruction. Laparotomy revealed a low grade peritonitis with pooling of the fibrinous exudate in the hepatic flexure, causing a paralytic ileus in this region. Further staphylococci were grown from the peritoneal exudate and from a blood culture. Following intravenous drip therapy and gastric suction and a further six weeks of antibiotics the ileus and obstructive jaundice gradually resolved.

The sequence of events seems to have been—Severe Group B incompatibility necessitating

three exchanges, following which the patient developed a pyelophlebitis and possibly a portal vein thrombosis. A peritonitis also occurred and gave rise to the paralytic ileus. There was an associated obstructive jaundice.

Discussion.—Group B incompatibility is seldom severe enough to necessitate three exchanges. Obstructive jaundice associated with hæmolytic disease of the newborn is not uncommon and is usually due to inspissated bile obstructing the intra- and extra-hepatic ducts. Sepsis following umbilical exchange transfusion seems to be very rare with only two other reports of it in the literature, although many more cases may occur.

Diastematomyelia.—J. P. M. TIZARD, M.R.C.P.

Girl, aged 3 years 6 months, was noticed at birth to have a tuft of long, fine hair overlying the mid-dorsal spine. X-rays displayed a picture interpreted as diastematomyelia. The 5th to 9th dorsal vertebræ and the spinal cord are widened; the disc spaces are narrowed and there is a vertical median bar of bone starting at the 5th vertebral body and extending downwards to the upper border of the 7th.

No operative treatment has been carried out and the child has at no time shown any defect of locomotion or of bladder control and there are no abnormal neurological signs.

Discussion.—The spinal column grows faster than the spinal cord and the development of neurological defect in cases of diastematomyolia is attributed to the increasing pressure exerted on the cord by the bony spine transfixing it. Most modern writers on this subject regard spinal cord damage as being sooner or later inevitable and therefore advocate early operation. For instance, Matson and his colleagues (1950) state that it is "good preventive medicine to carry out surgical treatment of diastematomyelia associated with spina bifida occulta at any time the diagnosis is made in early infancy and childhood". In most cases of diastematomyelia, however, the defect is found in the lumbar or lower thoracic region. Of 22 cases reported by Ingraham and Matson (1954) in only one was the defect above the level of T.8. It is obvious that the higher up the cord, the less is the difference in growth rate between cord and spine and it is suggested that a conservative policy may be justifiable in this case. The decision not to operate early was made in collaboration with Mr. Valentine Logue and the child has been, and will continue to be, re-examined at regular intervals.

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Brachial Plexus Palsy Associated with Soft Tissue Atrophy in the Scapular Region.—J. P. M. TIZARD, M.R.C.P.

Girl, aged 15 months. Pregnancy normal; uneventful vertex delivery. She was noticed at birth to have the following abnormalities: (1) Weakness of the left arm, due apparently to an upper trunk brachial plexus palsy (Erb-Duchenne type). (2) Various skin lesions: (*a*) About a dozen small (2–3 mm. diameter) faintly bluish shallow pits, mainly on the left side—limbs, trunk and upper lip; (*b*) two vascular nævi, one on each thigh; (*c*) an ill-defined, irregular patch of atrophic skin (4×3 cm.) attached to subcutaneous tissue above the left scapula.

The vascular nævi have now started to regress and the other skin lesions, although still present, are inconspicuous. There has been little or no improvement in the paralysis of the left arm. No abduction of the arm, nor supination of the forearm seems possible. There is some ability to flex the forearm. Hand movements are unaffected. There is wasting of the left deltoid and upper arm muscles and absence of the left biceps and supinator jerks. There is no obvious loss of pin-prick sensation. There is no sign of an upper motor neurone lesion in the legs to indicate cord damage and no evidence of sympathetic chain involvement (Horner's syndrome) to suggest root damage.

Discussion.—The prognosis in cases of birth palsy of the upper brachial plexus type is generally considered to be good, although recovery is by no means invariable. On the other hand, it is very unusual for the delivery of a baby with brachial palsy to have been entirely normal (Morison, 1938). It is suggested that the palsy of the left arm in this child was not due to stretching or other damage to the brachial plexus at birth, but to prenatal malformation associated with a similar process in the overlying subcutaneous tissue and skin.

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Acrogeria.—DAVID MORRIS, M.R.C.P.

Girl, born January 23, 1950. Both parents are healthy and there is no history of consanguinity. The pregnancy and the delivery were normal but the child was born prematurely without obvious cause; the birth-weight was 4 lb. 12 oz. Elder female sibling is alive and well and normal. A second sibling died in 1948 from tuberculous meningitis, no contact was found.

Progress had been normal from birth till 3½ years of age when she developed a tendency

to bruise easily and the parents became concerned over her "poor general condition". Blood examination, including bleeding and clotting times, was normal. The child appeared to lack subcutaneous fat over the whole body but particularly of the hands and feet (Figs. 1, 2, 3). These were emaciated and fleshless with the veins showing through the



FIG. 1.



FIG. 2.



FIG. 3.

thin and wrinkled skin similar in appearance to the hands and feet of old people. The descriptive label of peripheral ectodermal dysplasia was given at the time. Three years later Dr. G. B. Dowling identified the condition as acrogeria as described by Gottron (1940). Only two other reports of the condition could be traced in the literature, Gromzig (1951) and Bazex and Dupré (1955). There do not appear to be any other associated anomalies.

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Periodic Neutropenia—A Family Study.—T. J. PARKINSON, M.R.C.P., and B. W. MEADE, M.D. (for MARY J. WILMERS, M.D.).

Girl, aged 10 months when first seen with an ulcer on her lip which had failed to respond to local treatment (Fig. 1). A blood count showed hæmoglobin 8·9 grams/100 ml., total white cells 2,800 per c.mm., neutrophils 980 per c.mm. Three days later the neutrophils were 80 per c.mm. A diagnosis of agranulocytic angina was made and treatment instituted with antibiotics, Pentnucleotide, folic acid and a transfusion of fresh blood. Marrow biopsy showed maturation arrest of the myelocytic series. Gradually her condition improved and her neutrophil count rose to 8,260 per c.mm.

She remained well for almost a year, but then suffered another attack with ulceration of her mouth and vulva. Her neutrophil count fell to 777 per c.mm. Again she recovered with antibiotics and her neutrophil count rose to 6,120 per c.mm.

From then until the age of 7 the ulceration recurred, accompanied by malaise and variable pyrexia. At this time the diagnosis of periodic neutropenia was made on the basis of repeated blood counts. A typical cycle is shown diagrammatically in Fig. 2.

Other members of her family have had similar recurrent ulceration. Her father has been observed with ulcers and concomitant with one crop a neutrophil count of 1,312 per c.mm. was obtained. At other times his blood count has been normal.

Her aunt also has recurrent mouth ulcers. Two counts have been made which showed neutrophils at 2,000 per c.mm. and 2,280 per c.mm. respectively. Her grandfather has suffered from mouth ulcers but the only blood count recorded is normal, and we have been unable to study him during an attack.

Comment.—This child presents the clinical features and blood count of periodic neutropenia as described by Rutledge *et al.* (1930), Borne (1949), Embleton (1937), Barling (1948), Vahlquist (1946) and Moncrieff (1951). Her father presents a similar, though less well-documented picture, with attacks of mouth ulcers associated with neutropenia. Her aunt and grandfather appear to have the same condition.

The occurrence of this rare condition in more than one generation of a family does not appear to have been reported before.



FIG. 1.—Showing an ulcer seen in the first agranulocytic episode. Both the child and her father have recurrent crops of ulcers of this type.

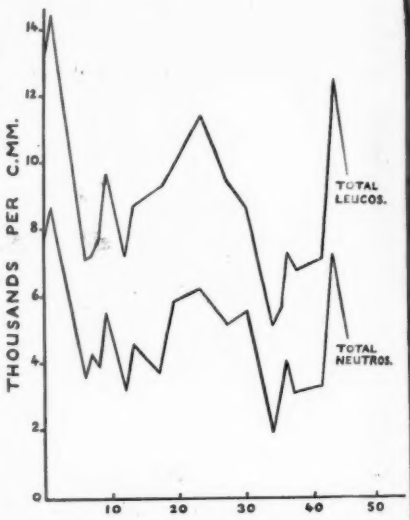


FIG. 2.—Showing neutrophil and total leucocyte counts, recorded for a seven-week period at the age of 7 years.

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Letterer-Siwe Disease Treated With Prednisone.—EVA A. FROMMER, M.B., B.S., D.C.H. (for W. MESTITZ, M.D.)

Girl, born 4.2.56, is the only child of healthy parents. The delivery was normal, at full term, birth weight 7 lb. 13 oz. and she was breast-fed. She was first seen at the skin clinic of the Royal Alexandra Hospital for Sick Children, Brighton, in March 1956, at the age of 7 weeks, with a rash of four weeks' duration. This failed to respond to treatment. About two months later a chest X-ray was taken, as the baby was seen to be cyanosed. The film showed widespread mottled infiltrations of both lungfields, with a suggestion of honeycombing particularly in the lateral view. The baby was referred to Dr. W. Mestitz who admitted her for investigation. She was now aged 5 months, had been weaned, but was not thriving as well as formerly. She had recently been coughing.

Weight was 12 lb. ½ oz., Temperature 98·8° F., pulse 130 and respirations 35 per minute. She was an ill-looking, snuffly baby; a rash of brownish-yellow, crusted papules and petechiæ covered the trunk and groins. High-pitched tubular breathing was heard over the base of the left lung posteriorly. The liver was just palpable, and the spleen enlarged to two finger-breadths below the costal margin, and hard. A few glands were felt in both groins.

The diagnosis of Letterer-Siwe disease was suggested, and confirmed by the biopsy of a wedge of skin, with several flat-topped papules (Fig. 1 A and B).

Histology.—The lesions are confined to the upper dermis. Each papule is formed by œdema and cellular infiltration of a group of papillæ; where this occurs the epidermis becomes thinned, the dermo-epidermal border becomes blurred, and there is "rat-tailing" of the rete partitions in a manner reminiscent of lichen planus. The infiltrate is composed mainly of large reticulum cells with a foamy cytoplasm; there are also neutrophil and eosinophil leucocytes and small lymphocytes; the latter types of cell tend to infiltrate the epidermis, as well as the dermis. It has not been possible to demonstrate whether or not lipoid is present in the reticulum cells, but even without this information, the presence of such cells as a major constituent of the infiltrate places this lesion in the Letterer-Siwe group of lipidoses.

Further investigations.—Hb 93%, white cell count within normal limits, platelets 22[illegible]000;

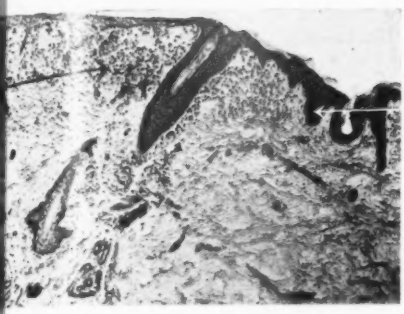


FIG. 1A.—Low-power view of the skin biopsy showing normal skin, a, and an area of infiltration, b.

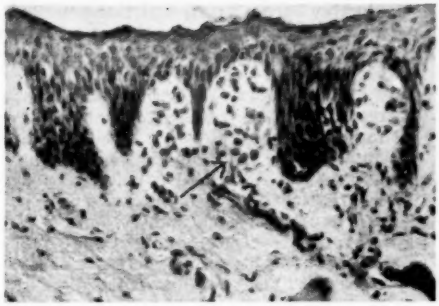


FIG. 1B.—High-power view of the area b, above, illustrating the character of the infiltrate. The arrow points to a group of histiocytes with foamy cytoplasm.

bleeding time 4½ min., clotting time 4 min. 10 sec. Blood cholesterol 250 mg.%, serum proteins 5·8 grams%, A/G ratio 2·4 : 1. X-rays of skull and skeleton: no abnormality.

Treatment with prednisone was commenced on 17.8.56, 2·5 mg. six-hourly. As the skin condition did not improve and the lung picture deteriorated the dose was doubled one month later. Following this there has been steady improvement, with quick resolution of the lung infiltrations, and gradual fading of the rash.

There have been several pyrexial episodes due to minor staphylococcal skin infections, which have responded to antibiotics. The child is thriving, and progressing normally. Some fullness of the face, and a double chin have developed recently, and the dose of prednisone was reduced to 5 mg. thrice daily; however, during a recent severe upper respiratory infection the rash became more marked, and there was some enlargement of the spleen; the dose was therefore increased to 7·5 mg. thrice daily, with beneficial results so far.

Comment.—It is now generally recognized that Letterer-Siwe disease, or infective reticuloendotheliosis, is closely related to Hand-Schüller-Christian syndrome (and eosinophil granuloma of bone), as pointed out by Wallgren (1940). It appears to be the form of the disease which manifests itself in infancy and early childhood. At this age it is more malignant, with a very poor prognosis, although occasionally spontaneous recovery has been reported.

Antibiotics have been tried, with moderate success, as have X-ray treatment and nitrogen mustard. The latest addition in the therapy of the disease is cortisone, and ACTH. Cox (1953) has described a case treated successfully with cortisone, and has reviewed this form of treatment (1955–56).

Our patient is being treated with prednisone, and we believe that her improvement is *propter hoc* and not *post hoc*. She was very ill on admission, and continued to deteriorate until treatment was begun. She improved soon after the dose was increased, with quick resolution of the pulmonary lesions. The rash is proving more obstinate, and the spleen slow to diminish in size. A similar progression of events was noted by Cox in his case; the last relapse shows that the scheme of treatment must be flexible, and the literature suggests that, on the whole, a high dosage is required and that the treatment must be maintained over a long period. We propose to reduce the dose slowly, guided by the clinical findings, and to discontinue it eventually if this proves possible.

We are indebted to Dr. R. I. K. Elliott for the section report, and photographs.

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POSTSCRIPT.—The baby subsequently deteriorated quite rapidly and in spite of increasing doses of prednisone she had several successive cyanotic attacks necessitating continuous oxygen therapy and died on March 12, 1957.—E. F.

Multiple Congenital Nerve Palsies.—CLIVE UPJOHN, M.D. (for J. N. O'REILLY, D.M.).

Boy aged 15 months. *History.*—Mother gravida 1. Pregnancy normal and full-term. Long first-stage labour lasting nearly 41 hours, when she was an emergency admission to another maternity hospital. On admission there, mother's cervix was only 3 fingers dilated and when full dilatation had occurred birth was assisted with a low forceps delivery.

Baby's condition at birth poor with blue asphyxia. Colour remained poor initially but responded to intranasal oxygen after a few hours. Birth weight 7 lb. 14 oz. He was very

"bubbly" from birth, and this persisted despite frequent extraction of mucus. Cyanotic attack developed at the onset of first bottle feed. Œsophageal atresia was excluded by passage of a catheter into the stomach. He remained bubbly and was transferred to St. Helier Hospital at 14 days of age.

On admission.—General condition satisfactory. Left facial paralysis, probably upper motor neurone type. Recurrent attacks of laryngeal obstruction occurred as a result of rapid collection of saliva and mucus in the nasopharynx. Lipiodol introduced into the nasopharynx was promptly aspirated into the trachea, giving a generalized bilateral bronchogram. A neuromuscular defect was suspected and he was seen by Mr. L. F. W. Salmon, E.N.T. specialist, who confirmed that the baby had a right palatal and pharyngeal paralysis, and direct endoscopy showed paralysis of the right vocal cord.

Progress.—Up to 3 months of age mucus and saliva continued to collect rapidly, causing frequent recurrence of respiratory obstruction requiring aspiration every five to ten minutes. After this time aspiration was required less frequently, varying from twenty minutes or longer, up to 6/12 of age, when there was a marked improvement, but aspiration was still required four-hourly before feeds until 8/12 of age.

All feeds were given by tube up to this age, when it became possible for him to take increasing amounts from a spoon; clear sterile fluids were given initially but he progressed quickly to milk and semi-solids by 9/12 of age. His subsequent progress was satisfactory and he was discharged home aged 11/12, weighing 23¾ lb.

His development is normal and he is a robust and very active child.

His condition was reviewed at 15/12 of age. Right pharyngeal paralysis persists. He weighed 28 lb. He swallows semi-solids most easily. He still chokes at times on liquids, and he has difficulty in swallowing any dry or solid food. Walking and talking well advanced.

Comment.—Initially this child's clinical condition was strongly suggestive of œsophageal atresia. After this had been excluded the alternative diagnoses were: (1) Neuromuscular abnormalities. (2) Tracheo-œsophageal fistula. (3) Sabre-defect in posterior laryngeal wall.

Investigation showed the presence of multiple cranial nerve palsies and it has not been possible to decide whether these were due to birth trauma or congenital failure of development. After this diagnosis the management became predominantly a nursing problem requiring constant attention for many weeks.

Peripheral Dysostosis.—S. D. V. WELLER, M.D., M.R.C.P.

Male, aged 15 years. Elder child of healthy parents. Father below average height, having short feet with high arches, but neither parent shows signs of peripheral dysostosis, and sister is also normal. No significant past illnesses, but wore arch supports between ages 5 to 10 years.



FIG. 1.

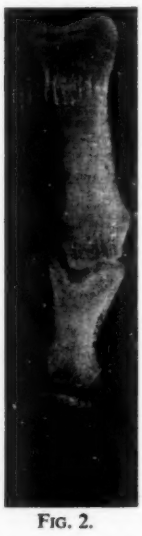


FIG. 2.

Presented in May 1953 with complaint of fingers becoming misshapen for five months. Deformity had been painless except during rubella in March 1953.

On examination (aged 11½ years).—Rather adult facies. Spindle swelling of fingers with some deviation, particularly at first interphalangeal joints. Short great toes. Negligible disability.

X-rays.—Conical epiphyses showing irregular central fusion, with metaphysis tending to grow over the lateral epiphyseal margins. This feature most obvious in proximal phalanges of great toes and middle phalanges of fingers. Dense epiphyses on some distal phalanges (a normal variant) (Fig. 1).

Progress.—Deformity has progressed painlessly

Present state.—All epiphyses fused in hands and feet (Fig. 2). Those previously normal have fused normally, as have those that were unduly dense. Abnormal epiphyses have fused, but look almost as if they have been absorbed into the cup which the metaphysis had previously formed about them. This has led to some obliquity at the interphalangeal joint.

FIG. 1.—X-ray of left middle finger; condition on 7.8.54.

FIG. 2.—Condition on 20.11.56.

Partial fusion has occurred at the knee epiphyses. All epiphyses are fusing prematurely and the patient has apparently stopped growing.

Section of Medicine

President—G. E. BEAUMONT, M.D., D.M., F.R.C.P., D.P.H.

[*November* 27, 1956]

DISCUSSION ON THE MANAGEMENT OF PATIENTS SUFFERING FROM PULMONARY TUBERCULOSIS

Dr. A. Brian Taylor: The aims of treatment of pulmonary tuberculosis were given by Livingstone (1955) as follows: (1) Permanent healing of the lesion; (2) Minimal loss of respiratory function; and (3) The attainment of these in the shortest time.

The indications for treatment and methods to be used are more controversial. Burrell (1930) in his Mitchell Lecture described mainly clinical evidences of activity. Nowadays radiological appearances have largely, perhaps excessively, superseded these. At the same time, morbid and histological characters, particularly of resected lesions, have influenced many towards a more aggressive and radical attitude, though the experience of the past has shown that tuberculosis can heal and may do so permanently in situ. The patient himself, with his personal problems, loses something of his importance. For instance, restoration of health is nowadays largely, though inadequately, defined as restoration of the ability to work—a reflection of the modern Welfare State. The length of treatment, especially of restriction of activity, becomes longer and longer, and at the same time intolerable.

It is necessary to plan the treatment to attain permanent healing at the first attempt. Second and subsequent periods of treatment are demoralizing and make return to useful work more difficult for the patient and his employers. The possibility of relapse has a strong influence on treatment, especially the prolongation of chemotherapy and the indications for surgery.

Early acute disease is, naturally, the most hopeful for treatment. Astonishing radiological clearing of the lungs can occur. Such complications as tuberculous laryngitis and tuberculous enteritis have almost disappeared.

Medlar (1955) divided the parenchymal disease into the non-necrotic and necrotic components. The former consists of a lobular pneumonia which can heal completely by resolution or by the formation of epithelioid tubercles which in time may heal by scar formation. This is the type of disease most responsive to the general care of the patient and the adequate administration of potent antibiotics.

Auerbach (1955) has suggested that compared with untreated disease, lesions after chemotherapy show rapid clearance of the perifocal reaction, with a thinner capsule, thinner walls of cavities and decreased pulmonary fibrosis and emphysema. This conforms to the notable clearing which can occur radiologically after early and intensive treatment with specific drugs.

In the necrotic component dissemination and cavity formation may ensue. The bacilli are particularly found in the necrotic material and may persist indefinitely and lead to relapse. Structural changes occur in the lung and cavity formation is notoriously difficult to heal. These give the chief need for additional surgical measures.

The frequent discovery of completely healed asymptomatic lesions by routine X-ray shows the common occurrence of the former process but when the lesions are of any size, their age and potential danger, by harbouring necrotic material with viable bacilli liable to dissemination, are difficult to assess. There is also the difficulty of distinguishing these lesions radiologically from the not uncommon pyocele secondary to bronchial tuberculosis (Clegg, 1953).

These latter lesions are obviously in a different category from the point of view of their persistence and danger as well as their lack of response to chemotherapy. Excision when feasible is especially attractive.

Two further considerations arise in connexion with drug treatment. One is the possibility of dispensing with prolonged and complete bed rest. An ill and toxæmic patient is obviously best in bed. An infectious patient is more easily restrained by restriction to bed. When, however, the acute stage is passed, toxæmia is absent, sedimentation rate normal, and symptoms relieved, how much rest is required? The possibility of treating indolent or recovering and favourable cases by long-continued drugs and slight modification only of normal life must be considered when risks of infection can be excluded. For the housewife, for instance, without whom the home can hardly be run, and for the University student there seem to be considerable advantages. The routine examination of Birmingham

University undergraduates at the start of each session reveals a few asymptomatic cases, apparently on the borderline of activity. To stop them working inevitably loses them a year in time, as they must wait for the next session if they are interrupted by more than a few weeks. This disorganizes them as well as the economic use of the limited places in the University. It seems possible that modification of working hours, avoiding violent exercise and chemotherapy, with close frequent supervision may be a reasonably safe compromise. Springett (1956) has shown that many minimal lesions do not relapse during simple observation and continued work. Black and Poole (1955) observed a number of round foci and found them stable and largely harmless.

The increasing tendency to continue a course of antibiotic drugs for at least a year after clinical quiescence seems most reasonable. When special hazards predispose to relapse more drugs may well be worth while. Respiratory infection and bronchitis are so commonly found immediately preceding a relapse that the winter months may be partly safeguarded by taking drugs if the urban life of a patient makes these dangers likely.

Surgery for pulmonary tuberculosis is mainly indicated for extensive structural changes in the lung, especially when cavities persist, and for nodular lesions.

Resection is most applicable for solid lesions, particularly more than 1 cm. in diameter such as result from the cold abscess (or pyocele), and if containing necrotic material with viable bacilli as described by Medlar (1955). They must be single or relatively few, and are more hazardous in unco-operative or stupid patients. Radiological appearances should not be an enticement to unnecessary surgery and removing healed safe lesions is not only pointless but may be dangerous. The disease can heal and extensive bilateral disease beyond the scope of resection often has to demonstrate this. Completely healed lesions removed and proved by histology to have been harmless are not infrequently found, and should be a reproach to the choice of surgery.

Chronic persistent thick-walled cavities, especially without much disease elsewhere and especially in the lower lobes, are as well resected.

Destroyed lungs, tuberculous bronchiectasis, localized atelectasis and chronic tuberculous pyopneumothorax are better removed.

The failed thoracoplasty, that is failure to obliterate a cavity or secure sputum conversion, is an indication for resection.

Early lesions, especially if small, localized and active, may be removed to shorten the patient's treatment instead of waiting for complete quiescence and the so-called "target point". Intensive antibiotics, of course, accompany and follow the operation.

Thoracoplasty in its various modifications has now been shown to be an effective and safe operation, leaving little functional disability and negligible deformity. Conversion of sputum occurs in a high proportion of cases, e.g. 80% of unselected cases reported by McHale (1949). In particular, it assists natural healing in situ while medical treatment continues and it can combat more extensive disease in the same lung or in the opposite lung. In fact, improvement of contralateral disease may follow collapse of the major lesion.

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Mr. W. P. Cleland: *Surgical Management of Pulmonary Tuberculosis*

My remarks will be confined to patients with pulmonary and bronchial disease. I will consider these aspects under three headings, viz.:

I. The indications for surgical treatment.
II. The scope of the investigations required when planning surgical treatment.
III. The type of surgery to be employed.

I. Indications for Surgical Treatment

These may be considered under the following headings:

(*a*) *Failure of the medical regime.*—In the initial stages of treatment one is not justified in withholding any reasonable therapeutic measure. This implies the administration of full doses of the antibiotics combined with bed rest. I see little point in employing intermittent streptomycin during the initial period of treatment and would much prefer that the patient should have daily streptomycin with both PAS and isoniazid until the sensitivities

have been determined. A period of between four and six months is generally accepted by the majority as sufficiently long to expect a good response to treatment. One can define, therefore, failure of the medical regime as the persistence of tubercle bacilli in the sputum and the presence of cavitation after four to six months of bed rest and adequate chemotherapy.

(*b*) *Early drug resistance.*—The occurrence of organisms resistant to one or more drugs on the first examination is increasing. Sterilization of lesions with prolonged chemotherapy is less likely to occur when the bacilli are resistant. These patients thus present a difficult problem. Owing to the likelihood of resistance to the remaining drugs developing, surgical treatment, if indicated, is often advisable at a relatively early stage in order to have the benefits of an antibiotic cover for the operation.

(*c*) *Residual lesions or sequelæ which are considered likely to give rise to trouble in the future.*—It is this group which arouses the greatest controversy, particularly since the widespread practice of resection. It is in this group also that the benefits of long-term chemotherapy are now being claimed. Residual lesions can be considered under a number of headings:

(i) *Residual nodules.* These, if large, and particularly when solitary (tuberculoma), do not present any real problem. The larger nodules are more likely to break down and less likely to heal firmly by fibrosis than the smaller foci. It is also sometimes difficult to be quite certain about the diagnosis in such cases. Smaller nodules present a more difficult problem, and each individual surgeon and physician has his own criteria for their removal. With the pathological and bacteriological investigations of surgical specimens being undertaken, it is hoped that a clearer idea of the indications for removal in relation to long-term chemotherapy will be forthcoming. Stewart *et al.* (1956), for instance, have shown that chemotherapy can sterilize both cavities and caseous foci irrespective of their size provided the organisms are sensitive to the drugs and at least twelve months' treatment is given.

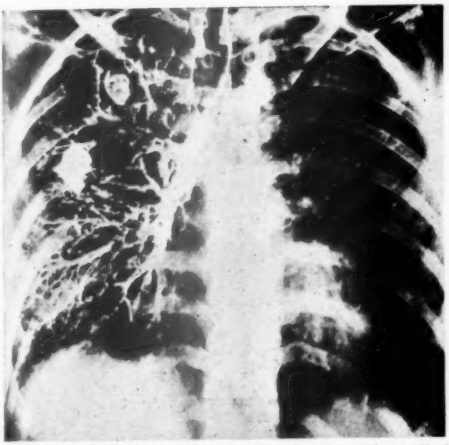


FIG. 1.—Right bronchogram showing two thin-walled cyst-like residual cavities filled with opaque oil. These cavities were not visible on the plain radiograph.

(ii) *Residual cysts.* Large, thin-walled cyst-like cavities are now appearing fairly commonly as a result of long-term chemotherapy. A number of these cysts fill readily with Lipiodol whilst others show no obvious bronchial drainage (Fig. 1). Keers *et al.* (1956) have indicated that, even after fairly prolonged periods of chemotherapy (up to fourteen months), complete histological healing may not occur and foci of tuberculous disease in the wall of the cyst can be found if an adequate search is made. Further evidence is required in such cases in order to guide one regarding their removal.

(iii) *Destroyed lobes.* The shrunken bronchiectatic and fibrotic lobe or lung following severe destructive lesions is often secondarily infected and a source of ill-health, and there is little doubt as to the necessity of its removal should conditions permit. The improvement in the patient's general condition, the elimination of cough and sputum and the cessation of hæmoptyses is most gratifying. The reduction in the respiratory reserve is negligible in these patients.

(iv) *Bronchiectasis.* The presence of bronchiectasis in an otherwise aerated lobe constitutes a more difficult problem. I think it is important to distinguish between the relatively minor bronchial dilatations occurring peripherally in relationship to a tuberculous focus and the grosser forms of bronchiectasis involving the whole of a lobar or segmental bronchus.

It is this latter group which we are considering here. In the lower lobe, these lesions are frequently secondarily infected and there is often a clear-cut indication for their removal. Similar lobar bronchiectasis involving the upper lobes is less likely to give rise to symptoms. Its presence, *per se*, does not constitute an indication for removal but these lesions sometimes

bleed and sometimes produce an intermittently positive sputum, and when such complications occur, there is a good indication for their removal.

(v) *Broncho-stenosis.* Complete obstruction of a stem bronchus is usually associated with damage and destruction of the lung tissue beyond the obstruction. Such damage alone will usually demand a formal resection. Occasionally a partial stenosis without lung damage is encountered, and if symptoms such as wheezing or attacks of bronchitis are present, then excision of the stricture (sleeve resection) should be undertaken.

(*d*) *Uncertainty about the diagnosis.*—The incidence of pulmonary tuberculosis in middle-aged males has shown a definite increase of recent years. This age group unfortunately carries a high lung cancer risk—a risk which is rising with the steady increase in the disease. These factors throw a great responsibility on the chest physician not only to make a positive diagnosis of tuberculosis but to exclude the presence of a cancer. It is imperative to seek bacteriological confirmation by all possible means and until such confirmation is obtained the diagnosis of tuberculosis should be suspect. The problem is particularly acute in those patients, often brought to light by miniature mass radiography, who have solitary rounded lesions. Tomography may provide strong circumstantial evidence in favour of tuberculosis in the presence of calcification or of satellite lesions. The problem is not made any easier by the not infrequent occurrence of cancer and tuberculosis in the same patient. If there is any doubt about the possibility of cancer, a thoracotomy is completely justified.

Case I.—J. D., male, aged 47. Admitted to hospital in July 1956 following a mass miniature radiographic finding of a rounded lesion at the right apex (Fig. 2). Tubercle bacilli were found in a smear from the sputum on one occasion and these were subsequently cultured. Tomography showed an irregular solid focus without cavitation, calcification or obvious satellite lesions (Fig. 3). He was given PAS and isoniazid for three months but both the straight X-ray and tomographs showed that the lesion was larger. Accordingly thoracotomy was performed and lobectomy carried out. The specimen (Fig. 4) showed a carcinoma (squamous cell). There was no evidence of a tuberculous lesion in the operation specimen.

(*e*) Surgery may be indicated at a relatively early stage in order to reduce the total length of treatment and enable the patient to get back to work with a reasonable degree of certainty at a specific date. It is usually possible to decide fairly accurately how long it will be after an operation before the patient can return to work. Such forecasting is less certain with medical treatment alone and there is always the possibility of having to employ surgical measures at some later date, although here again long-term chemotherapy is altering the picture appreciably.

(*f*) Patients who have to live abroad under unfavourable conditions can often be rendered more stable and better able to carry on if they have had the advantages of surgical treatment.

II. Pre-operative Investigations

It is unnecessary to underline the importance of an adequate period of observation and treatment with bed rest and chemotherapy before surgical treatment is contemplated. There is good evidence to indicate that the success of surgery is enhanced and freedom from complications is increased if a negative sputum is obtained before an operation is carried out. Should such negativity be unobtainable, the advantages of bacterial sensitivity to drugs, and the disadvantage of bacterial resistance with regard to post-operative complications are also well known.

In the planning of an operation, it is becoming more and more important to determine the precise extent and nature of the pathological lesions present. A complete survey of all earlier films, and the use of both lateral and antero-posterior tomographs is well known. From the surgical point of view, lateral tomographs are often of more value than antero-posterior tomographs because they enable an anatomical localization of lesions to be made more accurately.

The value of bronchography and the potential importance of pulmonary-function studies when planning surgery.—For the past year or more, I have had bronchograms performed on the majority of patients undergoing surgical treatment and on many occasions have demonstrated the presence of unsuspected bronchial lesions which have materially influenced surgical management. The presence of extensive bronchiectasis in an upper lobe which has residual nodulation or cavities, would strongly support a decision to resect the lobe rather than collapse it. Alternatively, the presence of widespread scattered, and perhaps even mild bronchial dilatation in patients with a localized lesion, would make one favour collapse therapy rather than surgery unless the whole of the involved bronchi could be removed.

Case II.—A. F., female, aged 30. This patient had a three-year history of pulmonary tuberculosis with bilateral apical disease. In June 1956 she was submitted for surgical treatment because of a recent relapse with a positive sputum. An X-ray (Fig. 5) showed infiltration in the left upper

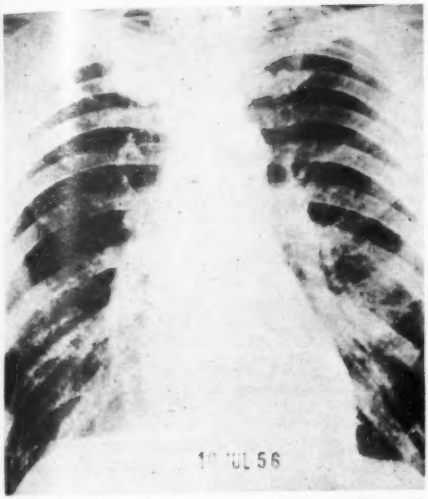


FIG. 2 (*Case I*).—Postero-anterior radiograph (July 1956) showing rounded shadow at the right apex.



FIG. 4 (*Case I*).—Specimen of right upper lobe showing typical peripheral type carcinoma.

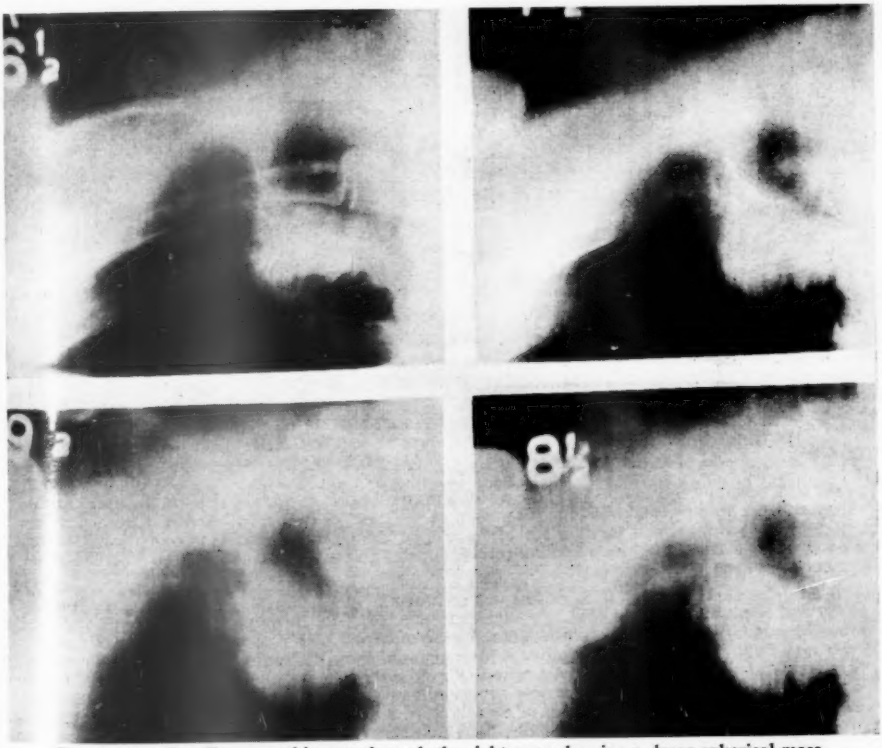


FIG. 3 (*Case I*).—Tomographic cuts through the right apex showing a dense spherical mass without calcification or satellite lesions.

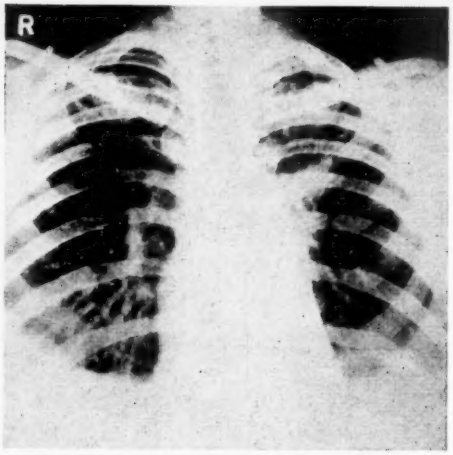


FIG. 5 (*Case II*).—Postero-anterior radiograph showing bilateral apical infiltration.

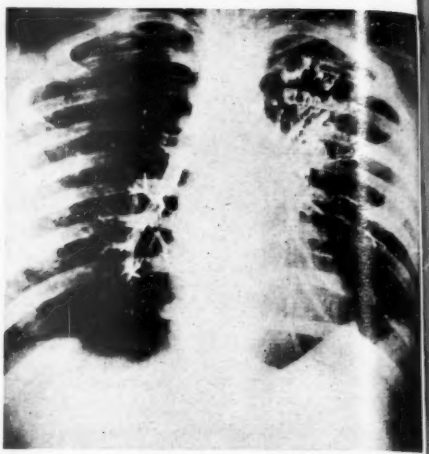


FIG. 6 (*Case II*).—Antero-posterior bronchogram showing gross dilatation of the upper lobe bronchi.

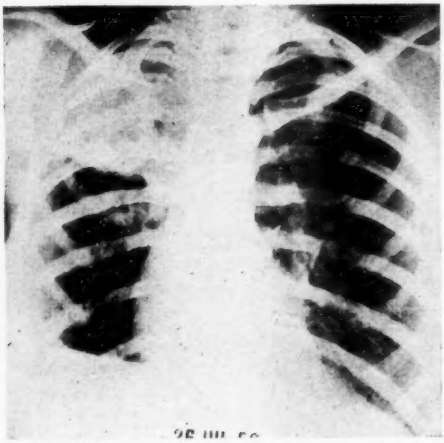


FIG. 7 (*Case III*).—Postero-anterior radiograph (July 1956) showing consolidation of the right upper lobe. The lower lobe appears normal.

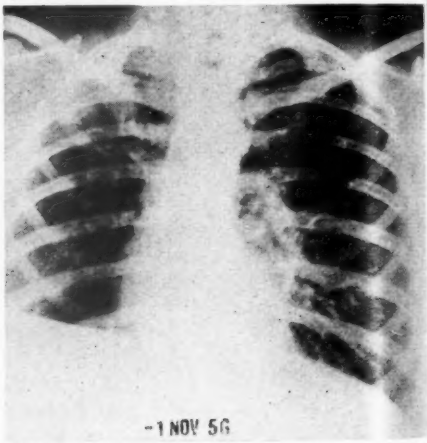


FIG. 8 (*Case III*).—Postero-anterior radiograph (November 1956) after four months' chemotherapy showing considerable clearing of the upper lobe consolidation. Residual nodular disease remains. There is no obvious cavity.

zone with several small cavities. There was infiltration but no cavitation at the right apex. At this stage collapse therapy was contemplated in view of the presence of bilateral disease. Bronchograms (Fig. 6), however, showed that the whole upper lobe was shrunken and bronchiectatic. Collapse therapy might have given disappointing results in such a case and accordingly an uneventful left upper lobectomy was carried out.

Case III.—G. I., female. This patient was admitted in July 1956 with a consolidated right upper lobe and a positive sputum (Fig. 7). She responded well to chemotherapy and an X-ray four months later (Fig. 8) showed considerable improvement but still a good deal of residual nodular disease though the sputum was negative and tomographs showed no cavitation. Resection was contemplated at this stage but a bronchogram (Fig. 9) showed not only gross bronchiectasis in the damaged right upper lobe but extensive bronchiectasis in the middle and lower lobes. Resection would have necessitated the removal of the whole lung which was not considered to be warranted as a prophylactic measure. Accordingly, long-term chemotherapy was instituted and the question of surgical treatment was deferred.

In a number of instances, completely unsuspected bronchiectasis has been demonstrated in the apical lower segment in patients with upper lobe disease where a resection was contemplated. I believe that leaving such a segment in the body, possibly with a raw upper surface, is responsible for some of the post-operative complications. In such cases, the apical lower segment should be removed in addition to the upper lobe, or resection should not be carried out at all.

Bronchography has been entirely safe and there has been no suggestion of spread of disease following its use. It is an investigation which has important bearings on the nature of surgical treatment which is to be carried out.

Pulmonary function studies are, at present, of limited value. The over-all function can be quite accurately determined by simple clinical tests and interrogation.

Bronchospirometry gives valuable information about the difference in function of the two sides, but the method is somewhat limited. The development of methods for determining the function of individual lobes should be of tremendous assistance in the difficult problem cases. Such detailed lung function studies will be of immense value when they can be applied to clinical problems.

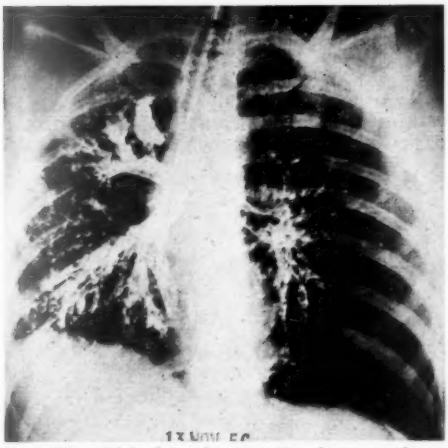


FIG. 9 (*Case III*).—Right bronchogram showing gross bronchiectasis of the right upper lobe.

III. Methods of Surgical Treatment

Most people will agree that the ideal treatment is resection but in varying proportions of cases the ideal treatment cannot be carried out, and alternative methods must be employed because they are safer. Resection has the advantage that it removes the bulk of the disease and it does not interfere with the function of the adjacent normal lung. A surgeon has to aim at removing all the obvious or gross disease, and it is for this reason that fairly complete investigations with tomography and bronchography are required before operation. The risks of complications if much disease is left behind are appreciable and, under these circumstances, many surgeons prefer to carry out some form of collapse therapy. The complications of resection are, on the whole, more serious than those of collapse therapy, and although not common, they carry a much higher mortality and morbidity rate.

The complications concerned are bronchopleural fistulæ, empyema and spread of tuberculous disease. These complications are higher amongst the sputum-positive cases and amongst those who have developed bacterial resistance. These complications must always be borne in mind when considering possible surgical therapy.

The contra-indications to resection are:

(1) Active or extensive disease on the same or opposite side which would not be included in the resection.
(2) Poor respiratory reserve.
(3) The presence of chronic bronchitis, emphysema or asthma.
(4) In the elderly.
(5) In those with active endobronchitis.

The alternatives to resection can be considered under the heading of thoracoplasty or one of the modifications, such as Holst thoracoplasty, Björk thoracoplasty or plombage. The very fact that thoracoplasty, or its modifications, is employed as an alternative to a resection where the latter is contra-indicated, means that it is never really legitimate to compare the results of the two forms of treatment except where such cases can be regarded as truly comparable.

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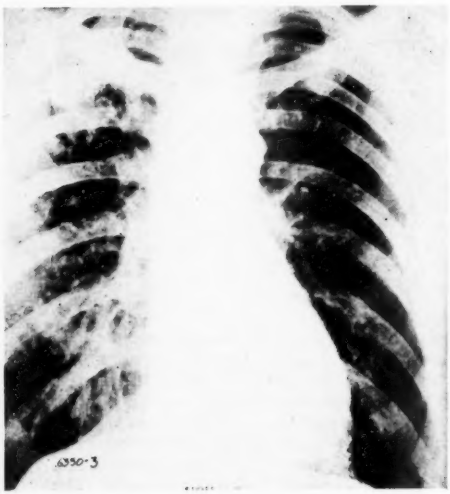
Dr. Peter Stradling: *The Chest Clinic Management of Pulmonary Tuberculosis*

The modern chest clinic has wide duties relating to the diagnosis and management of many chest conditions but the following brief remarks are restricted to its activities in relation to pulmonary tuberculosis.

The majority of tuberculous patients and their families can be managed solely from a chest clinic without reference to sanatorium, but an efficient chest clinic must provide, as an integrated whole, preventive, diagnostic and treatment services.

DIAGNOSIS

The prognosis for an individual tuberculous patient varies with the extent of the lesion when first discovered; Springett (1956) has recently confirmed this even for minimal lesions. Still not fully realized, however, is the possibility of rapid spread, particularly in young adults (Fig. 1A, B).



A



B

FIG. 1A and B.—The radiographs of a young man (R. N.) who declined treatment. A, on diagnosis; B, four months later.

Diagnosis at the earliest possible opportunity is thus a vital and self-evident clinical necessity. But prompt diagnosis is equally important administratively because the simple treatment methods that are then effective lead to a minimum of social disturbance. The first duty of a chest clinic, as stressed by Toussaint and Pritchard (1944), must thus be to provide diagnostic aid to General Practitioners from whom are referred, either directly or via hospitals, by far the largest proportion of new cases of pulmonary tuberculosis.

To assist early diagnosis a most important addition to ordinary consulting clinics is a freely available chest radiography service for practitioners. Such group radiography is a very sound diagnostic method because it is unusual for disease to pass the early stages

without the patient experiencing recognizable symptoms. I find about 25% of the films are abnormal and a great variety of conditions are revealed (Table I).

If such a routine radiography service is to be of high standard certain precautions must be taken. In the first place the human error inherent in the reading of all radiographs must be reduced as far as possible so that lesions shall not be missed. This can be attained in part by dual independent reading of the radiographs. In addition there is a proportion of tuberculous lesions the shadows of which are difficult to see because they become involved in those cast by the bony thorax. These can usually be revealed by a lordotic view which also prevents many unnecessary recalls. It is thus a good routine to take two views and to practise their independent dual reading (Stradling and Johnston, 1955). 10% to 30% of lesions will be missed if this is not done.

A routine radiography service should form a vital part of the National Health Service and be provided in every chest clinic. Prompt diagnosis means easier prevention and simpler treatment.

TABLE I.—A BRIEF ANALYSIS OF THE FINDINGS IN THE X-RAY SESSIONS HELD AT HAMMERSMITH CHEST CLINIC DURING 1955

X-ray Sessions: 1955

Total No. of patients X-rayed		3,034
Found normal	.. ..	2,263
Found abnormal	.. ..	771
Abnormalities		
Pulmonary tuberculosis	.. 26	(0·9%)
Carcinoma of bronchus	.. 15	(0·5%)
Pneumonia	 125	(4·1%)
Cardiovascular abnormalities	 142	(4·7%)
Miscellaneous abnormalities	 292	(9·6%)
Diagnosis pending	.. 143	(4·7%)
Lost sight of and transferred	 28	(0·9%)
	771	(25·4%)

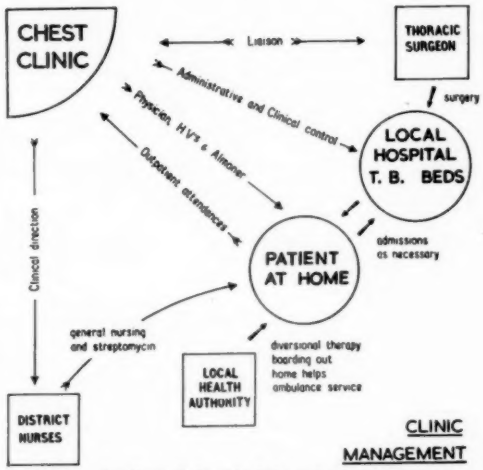


FIG. 2.—Outline of the administrative arrangements for operating a clinic management service.

(Reproduced from Stradling (1955) by kind permission.)

PLACE OF TREATMENT

The aim of treatment in a case of tuberculosis is not only the repair of pulmonary damage but rapid return of the patient and his family to social independence: this implies action on a much wider front than pure therapeutics and it is obvious that we must choose that method of treatment which is not only successful but involves the least possible disturbance to family and working life. Logically this implies that part or all of the treatment should be on a domiciliary basis: but it is not necessary to demand too high a standard of the home. Soon after the last war long waiting lists for sanatoria often enforced treatment outside these institutions. The results of such action, even before chemotherapy, equalled those of sanatoria (Stradling, 1951, 1955). Now chemotherapy has proved so powerful that a combination of local hospital, domiciliary, and out-patient treatment (for which I have coined the phrase "Clinic Management"), is an entirely acceptable alternative to sanatorium. The scheme is outlined in Fig. 2. The extent to which such a service can handle the local problem, even without an adequate number of local hospital beds, is indicated in Fig. 3.

I believe such Clinic Management to be the method of choice: apart from monetary saving, the advantages are great. There is continuity of medical treatment so important to both patient and physician. Long separation from the realities of life, so common in sanatoria, is avoided, thus abolishing the need for prolonged rehabilitation. The patient derives comfort and inspiration from the frequent visitors received when he is in the local hospital, and is not separated from his family at all when managed at home or as an out-patient. In short he is happier than in sanatorium.

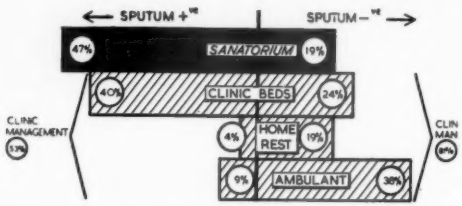


FIG. 3.—Methods of management used for the 114 new notifications in 1955. For those patients entering sanatorium the reason for admission was in every case an unsatisfactory home at a time when the local hospital beds were full.

The problem of returning to work is also diminished. The minimal disruption of social life enables the majority of patients to return quite quickly to their previous employment unless this is strikingly unsuitable. In more difficult cases the clinic Almoner (and Disablement Resettlement Officer where necessary) plays a vital part in assisting early re-employment before the patient becomes work-shy.

METHODS OF TREATMENT

Small lesions of rather doubtful or low activity form a special and increasingly important group. 40% of my new cases now have disease involving less than one radiological zone, and during the last five years the proportion of patients presenting with a positive sputum has steadily fallen (72% in 1951; 38% in 1955).

With such patients, who often feel well, it is of the utmost importance to avoid unnecessary disruption of their normal family life: it is so easy to produce neurosis which is far more troublesome than minimal tuberculosis. One should remember also that there is always a good chance of the patient recovering if his disease were never discovered. The many calcified lesions seen in routine X-ray surveys bear witness to this fact. On the other hand, particularly in the younger age groups and as already shown in Fig. 1, such lesions can advance in an unpredictable and rapid fashion.

Here then is a group ideally suited to ambulant chemotherapy. It is my practice with these individuals, after taking laryngeal swabs, to start such treatment as a therapeutic trial: often without interrupting their work. If, after some weeks, the lesion is smaller, then it was obviously active and treatment was indicated. But since it has improved, treatment is effective on an ambulant basis and there is no need to change it.

Overtly active disease in a sick patient presents a greater problem and needs a much more comprehensive service than the simple dispensing of drugs to an out-patient. Nevertheless, on a background of chemotherapy, this can be completely and successfully provided under Clinic Management.

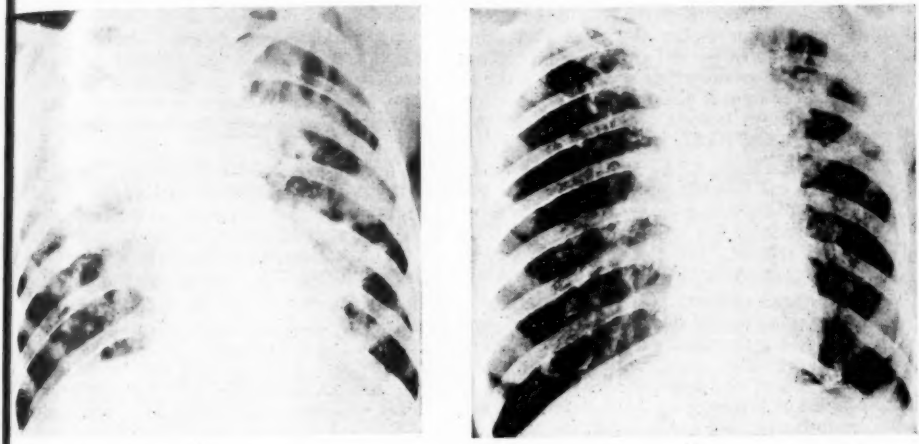
All patients, when enough "clinic" beds are provided, can be treated either in hospital, at home or ambulant, according to social circumstances and disease activity. It is the latter which is often difficult to assess and a valuable biochemical aid, considerably more accurate than the E.S.R., has recently been demonstrated in the albumin/a_2-globulin ratio obtained from serum electrophoresis (Gilliland *et al.*, 1956). This ratio falls progressively as disease becomes more active and correlates well with careful clinical assessment.

A fundamental issue in the medical management of tuberculous patients is whether bed rest is any longer essential. The final answer must await a properly organized, statistically valid trial involving larger numbers of patients than can be provided by one clinic area. Nevertheless, my clinical impression is that bed rest is no longer essential for the tuberculous provided they do not feel ill. Some of my patients, treated on an ambulant basis, even with obviously active or cavitating disease, have done so well that I wonder whether those remaining in bed are doing so unnecessarily.

The management of tuberculous patients can thus be undertaken outside sanatoria with chemotherapy replacing bed rest as the basic treatment. But here I would stress the importance of *multiple* drug treatment. It is my practice to give all three anti-tuberculous drugs in full daily doses until the bacterial sensitivities to them are known; 5% of newly diagnosed and previously untreated patients now excrete bacilli resistant to one or more of the three anti-tuberculosis drugs (Fox *et al.*, 1957). If thus found suitable, daily streptomycin + isoniazid alone are then usually continued for three to six months before PAS + isoniazid are substituted as a more convenient combination for the trustworthy ambulant patient. Many patients, however, continue daily streptomycin + isoniazid for

very much longer, Intermittent drug therapy (particularly one intermittent with the other continuous) is *not* employed in view of the risk of resistant bacterial strains emerging.

In many units chemotherapy has practically replaced artificial pneumothorax and pneumoperitoneum. Even advanced cases, usually quite unsuitable for surgery, do remarkably well on prolonged drug treatment alone or in combination with cortico-steroids (Fig. 4A, B).



A B

FIG. 4A, B.—The radiographs of a young woman (R. M.). A, on diagnosis; B, three years later. Desperately ill on diagnosis with tuberculous meningitis in addition to the extensive pulmonary disease, she received daily streptomycin, para-aminosalicylic acid and isoniazid for eighteen months. Although breathless she has been sputum-negative since completing her first three months of treatment and is again managing her home and family.

When suitable facilities are available surgical cases can also be managed well outside sanatorium. Major operations were performed by Mr. Cleland or members of his team on 58 tuberculous patients in my small 27-bedded unit over a recent five-year period. These included 23 resections, 15 thoracoplasties, 25 plombage operations and a small miscellaneous group. No serious complications occurred and only one patient was not quiescent a year after operation.

All surgical treatment is undertaken on a background of continuous chemotherapy which is maintained long after a patient returns to work. But a decision on surgery (now most often resection) is usually reached within three to six months of diagnosis so that work is resumed as soon as possible. Chemotherapy is so successful, however, that I sometimes wonder whether surgery is offered too frequently.

DIFFICULTIES

Two points need special consideration. In the first place there is the danger of infection to contacts if the sputum-positive patient is managed at home. But the preventive work of a chest clinic can be very effective. In the worst cases the danger is overcome by admitting the patient to the local hospital tuberculosis ward from diagnosis until sputum conversion is obtained. During this isolation period BCG is given to the tuberculin-negative contacts. Health Visitors are invaluable in persuading contacts to attend the clinic and in teaching how to avoid infection. Although modern chemotherapy rapidly renders a patient negative, the proper disposal of sputum from the infectious home-bound patient is still of importance and the Miltherex method is probably the best available at present (Stradling, 1953).

In this way the infectivity of tuberculosis can be very greatly reduced. Support to such a claim is given by the observed drop in the number of cases of active tuberculosis found by contact radiography at Hammersmith during the last few years: 7·5 per thousand films taken in 1951 falling to 1·0 per thousand for 1955. Furthermore during 1952 over half of the 23 contacts notified had developed their disease *subsequent* to the notification of the index case while in 1955 all of the 6 contacts notified were discovered at their *first*

attendance immediately after the diagnosis of the source case. The great improvement in the contact *follow-up* picture is probably due partly to the protection afforded by the BCG given to all tuberculin-negative contacts since 1950, and partly to the reduction of infectivity following the wider use of chemotherapy. The lesser drop in the number of contacts notified on *first* examination is probably a reflection of the earlier diagnosis being obtained. These findings stress the continued vital importance of the first contact examination but justify a more selective attitude to continued contact follow-up.

The most serious criticism that can be levelled at the management of the tuberculous as out-patients is the fact that chemotherapy is not closely supervised. There is the possibility of a patient either taking too small a quantity of a drug (particularly PAS) or of omitting it altogether, thus risking the emergence of resistant strains of tubercle bacilli. Such a criticism is not unique to out-patient therapy, however; to a lesser extent it can also be levelled at hospitals, where it is not always possible to supervise the consumption of every dose of PAS.

But even under Clinic Management much can be done to circumvent the danger. Health Visitors are constantly encouraging the patients to report any difficulties with the drugs instead of deceiving the doctor. Much time is spent on careful explanation to the patients; explanation of the importance of dual drug therapy regimes in obtaining results and preventing relapse. Where there is doubt about the trustworthiness of an individual, isoniazid can be given at the time of a streptomycin injection when the nurse can see that it is swallowed.

To those patients at work the factory medical organizations can be very helpful by undertaking to give daily streptomycin injections or supervising the consumption of cachets. District nurses will often give injections in the evening and it is possible to teach selected patients to give their own streptomycin. Ambulant oral chemotherapy can be offered as cachets or powders containing both PAS and isoniazid in appropriate doses; interruption of treatment then stops both drugs and so minimizes the danger of resistance. Urine tests are also available which reveal the presence of PAS. Some surprising results are obtained with routine urine testing (Simpson, 1956) but to retain the test's validity it is most important that the patients should not know its significance, which can be completely vitiated by a single dose of PAS taken before attending the clinic.

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Section of Orthopædics

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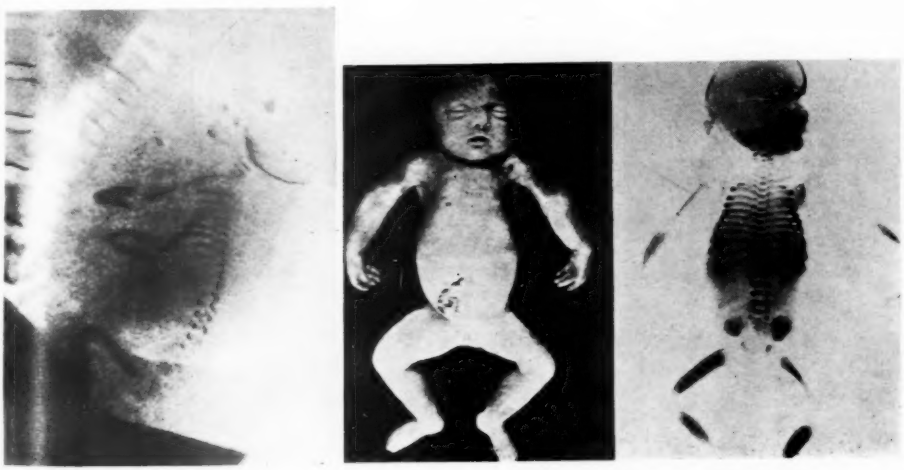
[*December* 4, 1956]

Infantile Cortical Hyperostosis; A Review of the Clinical and Radiographic Features[1]

By John Caffey, M.D.

New York City

Infantile cortical hyperostosis, hereafter called ICH, was first named and recognized as a separate entity in 1945 [1]; however, several observers, beginning with Röske in 1930 [2] had reported individual cases, similar to ICH, which they could not classify. The single Italian infant described by de Toni in 1943 is of special importance because he early recognized the congenital and regressive aspects of ICH. This disease is probably a new entity because, prior to 1930, there are no recorded descriptions, either clinical or radiographic, of a syndrome similar to ICH; it is unlikely that earlier clinicians would have overlooked its



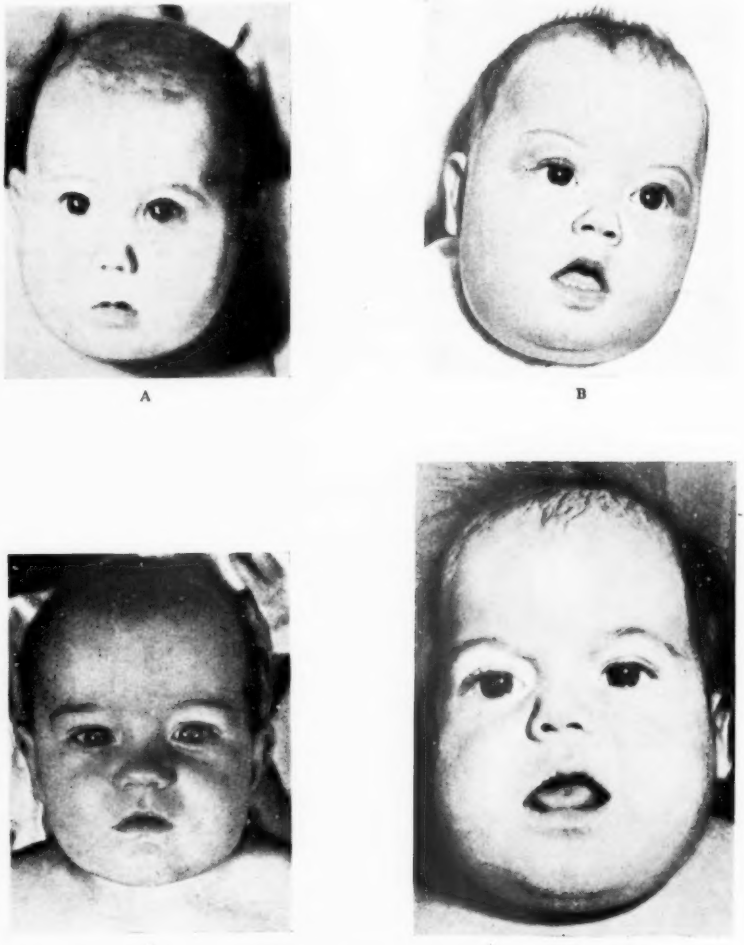
A B C

Fig. 1.—Prenatal infantile cortical hyperostosis in a fœtus 31 weeks of age. A, massive hyperostoses in the bones of the extremities in a lateral projection of the fœtus *in utero*. B, photograph of the dead fœtus after delivery by Cæsarean section. Swellings of the face and extremities are similar to those of postnatal ICH. C, rœntgenogram of the fœtus *ex utero* shows hyperostoses in the mandible, ribs, and tubular bones in the extremities which are similar to those found in postnatal ICH [C, Reproduced by kind permission; Bennett and Nelson, 1953].

[1]From the Departments of Pediatrics and Radiology, College of Physicians and Surgeons, Columbia University, and the Babies Hospital, New York.

striking and distinctive clinical and radiographic manifestations. With the passing of only a few years, it has become clear that the disease is not a rare one. Several cases are encountered every year in almost all of the larger pædiatric clinics in the United States and Canada, and almost every pædiatrician has seen one or more cases. One pædiatrician in North Carolina has recognized 11 cases in his own practice. Groups of cases have now been reported from all parts of the world from a wide variety of social, racial, and cultural environments.

The clinical and radiographic features have now been described in more than one hundred cases and it is likely that our knowledge of these aspects is almost complete. One of the most striking clinical features is the early age of the patient at onset of the disease. There are no valid cases in which the age at onset has been greater than 5 months; in our cases the mean age at onset is 9 weeks. In several cases ICH has been well developed at birth, both clinically and radiographically. Thick lesions in the long bones have been demonstrated *in utero* radiographically during the last month of gestation in two fœtuses which exhibited the classical disease postnatally [3]. Bennett and Nelson [4] found radiographic and anatomical



A B C D

FIG. 2.—Characteristic facial swellings of ICH infants 3 to 4 months of age; A, B, C, D.

changes, which simulated postnatal ICH, in a dead fœtus at the 31st week of gestation (Fig. 1). Similar findings were reported by Jenkinson [5] in a dead fœtus at the 24th week of gestation. The prenatal disease and limitation of onset of the postnatal to the first few months of life, both point to the importance of transmission from the mother as an important factor in pathogenesis of all cases.

The postnatal disease commonly begins suddenly with swelling of the jaw and face (Fig. 2) without premonitory signs. The infant usually becomes feverish and hyper-irritable at the same time. Conjunctivitis has preceded the facial swelling in several cases. In a few cases swellings have first appeared in the leg or arm, and the face became swollen three to four days later. In the thorax swellings may be present over the scapulæ, clavicles, or ribs on one or both sides (Fig. 3). In one case the parietal bone was swollen. Swellings in the extremities are accompanied by regional limitation of movement and tenderness but never by discoloration or œdema of the overlying skin, or local increase in heat. The regional lymph nodes have not been enlarged in our patients. The swellings are wooden-hard and



FIG. 3.—Characteristic facial swellings with multiple swellings in the right arm and hand, the left forearm and hand, the right thoracic wall and all of the right leg. This infant was 18 weeks of age; the disease began with right-sided facial swelling at 7 weeks of age. The intense swellings of the soft tissues have ballooned out the parts and split the superficial layers of skin in the left forearm leading to coarse desquamation. All of the bones beneath these swellings showed massive hyperostoses. There was no hyperostosis in the left humerus over which the skin is loose, with no swelling.

are deeply situated and fixed to the underlying bones; exact edges of the swellings are difficult to establish accurately, especially in the neck, where the swellings fuse with the thick fat infantile neck. Fever may be absent, or moderate and of short duration, or high and prolonged. Lack of fever is common when the disease is limited to the mandible. Mild or moderate pallor and anæmia are present at onset or develop early in the disease in more than one-half of the cases. The only laboratory finding of positive value is increase in the sedimentation rate of the red blood cells; roughly, this varies directly with the activity of the lesions. A moderate polymorphonuclear leucocytosis is the rule during the febrile phases. All bacterial, viral and immunological studies of the blood and biopsy specimens have given negative results. The urine and cerebrospinal fluid have been normal in all cases in which they were examined. Chemical and vitamin tests on the blood have also proved negative.

The clinical course of the disease is highly variable. In the mildest cases, facial swelling disappears completely after a few weeks. In moderate cases, with multiple swellings and tenderness, the clinical disease may last for several weeks or months with sudden appearance



FIG. 4.—Massive external cortical thickening of the mandible. The coronoid process is swollen and thickened but the neighbouring condylar process is not affected. Much of the cortical thickening is in the caudal direction (arrow). The infant was 3 months of age; facial swelling was detected clinically four weeks before this film was made. The mandible is filmed in oblique right lateral projection.

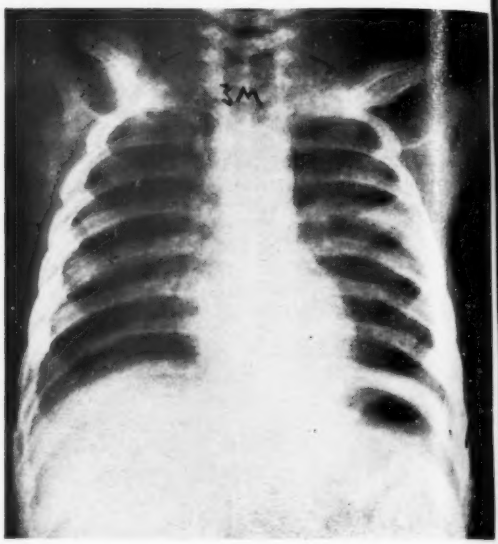


FIG. 5.—Multiple cortical hyperostoses in the clavicles and several ribs in both sides of the thorax in an infant 3 months of age whose face first became swollen during the ninth week of life.

of new swellings in one site while they are subsiding in other places. A single lesion may begin to regress and suddenly a new swelling will flare up in exactly the same site. The disease may be limited to two or three swellings for several weeks and then new swellings will appear suddenly in several other sites with rise in fever and sedimentation rate. These natural fluctuations make difficult the estimate of the efficacy of therapeutic agents. The swellings appear to regress by simple shrinkage; they never soften, penetrate the skin or discharge exudate of any kind. In some severe cases swellings have persisted for eighteen to twenty months without regression, and in others facial swellings and fever have recurred periodically for as long as seven years after complete subsidence of the original infantile attack. At least 3 patients have died.

The radiographic findings are identical wherever they are found. The cortical walls of the bones which underlie the swellings thicken externally (Figs. 4, 5, 6). These cortical thickenings are often found in bones where swellings have not been identified by palpation. In all of our patients in whom the mandible has been examined radiographically, both early and late, this bone has been thickened. The clavicles have been involved in about one-half of the patients; the tubular bones, including ribs, in about one-third; the scapulæ in about one-quarter; and more rarely, the metatarsals, the ilia, and the parietal bones. In 2 cases, scapular hyperostoses have been accompanied by ipsilateral eventration of the diaphragm (Fig. 7). In the chronic hyperostoses, the bones finally heal by reaming out of the hyperostoses which produces a thin-walled bone with dilated medullary cavity (Fig. 8). Acute and chronic hyperostoses in the rib are shown in Fig. 9. Patchy sclerosis of the mandible was evident in the mandible, six and three-quarter years after the onset, in one chronically recurring case (Fig. 10).

Morbid anatomy has been studied incompletely in biopsy specimens; necropsies have not been reported in the classical form of the disease; and there is a dearth of biopsies in the earliest phase of the swellings. All pathologists agree that the hyperostoses are made up of normal but immature lamellar bone. In many cases there has been no microscopic evidence of inflammation; in other cases the presence of cellular infiltrates has suggested inflammatory reaction. There is no anatomical evidence that subperiosteal hæmorrhage is a factor in the cortical thickenings. In the acute disease the periosteum is loose and thickened and often has a gelatinous character with many mitotic figures in the cells. This feature has led to the erroneous diagnosis of sarcoma in several cases, especially in specimens taken from the



A



B

FIG. 6.—Radiographs of the cortical hyperostoses in: A, the humerus and ulna of an infant 11 weeks of age whose face first became swollen at 2 weeks of age; B, in the femora and tibiæ of an infant 14 weeks of age whose face first became swollen during the seventh week of life. The absence of changes in the metaphyses and epiphyseal ossification centres readily differentiates this disease from scurvy.

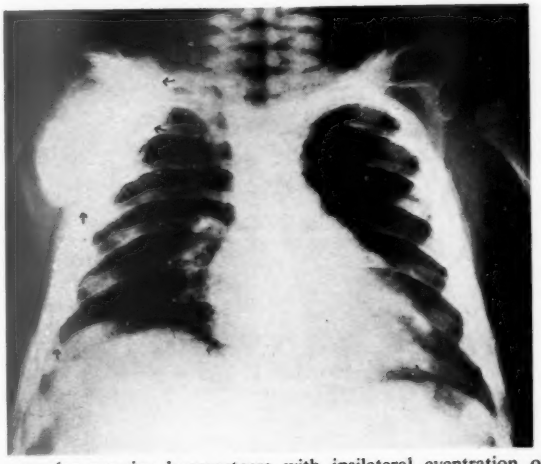
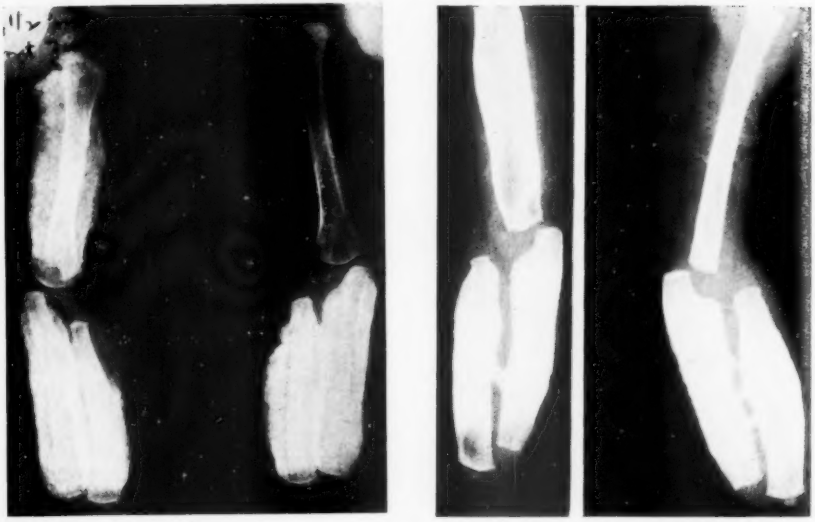
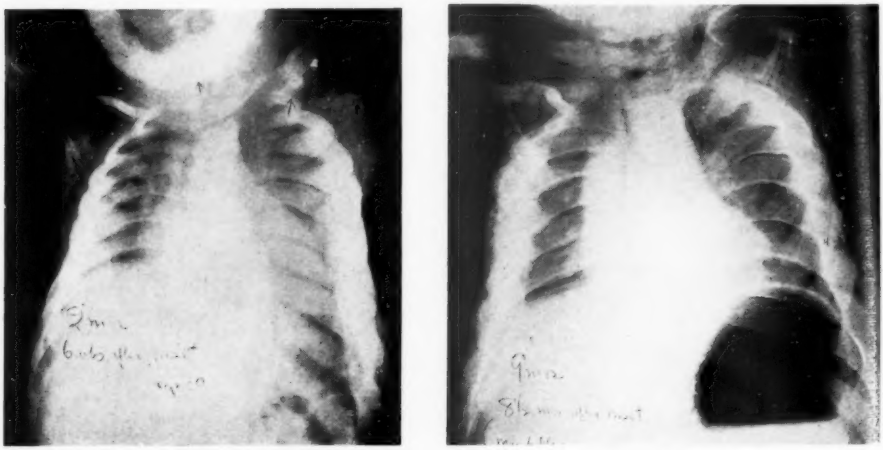


FIG. 7.—Right scapular massive hyperostoses with ipsilateral eventration of the diaphragm (arrows) of an infant 9 weeks of age who had been ill three weeks when this film was made. We have seen one other infant with ipsilateral hyperostoses of the scapula and eventration of the diaphragm. Both clavicles and several ribs on both sides are also thickened.



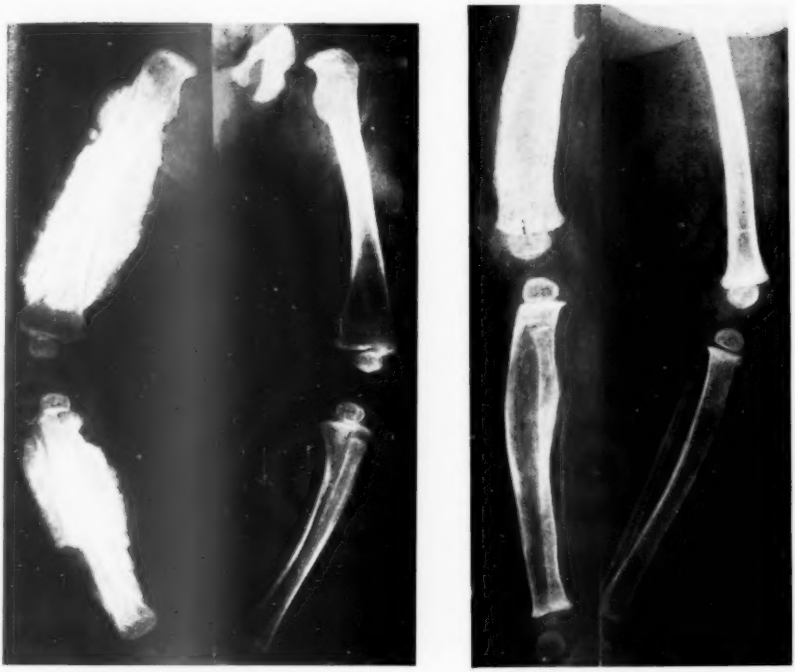
A B

FIG. 8.—Acute and chronic ICH with persistence of bone lesions for more than 29 months. The disease began at 7 weeks of age with facial swellings and rapidly extended to the thorax and extremities (*see* Fig. 3). A, arms at 4½ months show massive cortical thickening of the right humerus, both radii and both ulnæ. In the forearms, impaction of the thickened bones has dislocated the radius out of the elbow on both sides. B, in the arms at 12 months, the bones are still greatly enlarged in girth; bridges of bone anchor each radius to its ulna. Each radius is dislocated out of its elbow. The right humerus is still greatly enlarged but its hyperostosis has been partially reamed with corresponding increase in its medullary cavity. (*Continued on page 15.*)



A B

FIG. 9.—Acute and chronic hyperostoses in the ribs. A, at 2 months, six weeks after first facial swelling. All of the ribs on the left are massively thickened and sclerosed; the intercostal spaces are correspondingly narrowed. In the right ribs there are similar but less marked thickenings. The first and second right ribs are normal. The left clavicle and scapula are thickened and sclerosed. B, at 9 months the ribs on both sides are still massively swollen and the intercostal spaces are narrowed. These bulky ribs in contrast have thin cortical walls and greatly dilated marrow cavities in contrast to A. At 18 months, the findings were slightly less marked than in B.



C D

FIG. 8.—In C, legs at 4½ months, there are massive rough hyperostoses in the right femur and right tibia. In the left leg where there were no soft tissue swellings (*see* Fig. 3), there are no hyperostoses. In D, legs at 15 months, the hyperostoses in the right femur, tibia and fibula have largely disappeared owing to erosion of the thickened cortical walls from within, which has resulted in bulky bones but with thin cortical walls and correspondingly large medullary cavities. At 32 months, these thin-walled bones had been restored to almost normal shape; the medullary cavities had shrunk toward normal, and the cortical walls had re-thickened to approximately two-thirds of their normal thickness.

thickened scapula. The mucinous thickening in the periosteum usually extends directly into the neighbouring tendons, fascias, and intermuscular septa. In specimens taken several weeks after the onset, extensive muscular necrosis with fibrous replacement has been demonstrated. Sherman and Hellyer [6] found obliterating intimal proliferations in the regional small arteries; some think the arterial lesions are primary.

Although much has been learned about the clinical and radiographic manifestations of ICH, causation and pathogenesis have become even greater puzzles with the study of more cases. Numerous causal agents and mechanisms have been suggested but all have been found wanting—bacterial infection, viral infection, allergy, trauma, hormonal disturbance, collagen disease, and genetic transmission. The identification of the well-advanced disease *in utero* and at birth, and the limitation of the age of onset after birth to the first five postnatal months all suggest that the mother is the source of the disease. It is my belief that study of the mothers will finally unravel this baffling problem of the cause and pathogenesis in the infant.

Treatment was generally symptomatic until it became evident that the disease is occasionally fatal and not infrequently recurrent and chronic, sometimes with crippling residual changes. The adrenocorticosteroids are highly effective in all phases of the disease and we believe all patients should be treated in view of the uncertain prognosis in all cases, owing to the rapid and unpredictable fluctuations in the disease. Cortisone should be given in doses of about 200 mg. daily during a period of two to three weeks. Recurrence is likely when the cortisone is stopped at the end of one or two weeks. Dosage should be reduced gradually to prevent rebound phenomena which have been severe after sudden stoppage of the



A



B

FIG. 10.—Chronic recurrent ICH of the mandible from the third month to the seventh year. At 3 months the patient had the classical severe scattered disease. After several weeks the disease subsided but later, at intervals of three to six months, swellings of the jaw recurred. In these lateral oblique projections of the mandible, the right side of the bone (A) shows a severe patchy sclerosis and the left side (B) is normal radiographically.

steroid. With proper treatment desperately ill patients become asymptomatic after a few days. External swellings gradually subside and the radiographic changes may be visible in the bones for several months after complete clinical cure.

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Section of Urology

President—CUTHBERT E. DUKES, O.B.E., M.D., M.Sc., F.R.C.S.

[*October* 25, 1956]

"Behind the Scenes in Urology"

PRESIDENT'S ADDRESS

By CUTHBERT E. DUKES, O.B.E., M.D., M.Sc., F.R.C.S.

I AM privileged to be the first pathologist to be elected President of the Section of Urology. This Section of the Royal Society of Medicine is thirty-six years old. Sir Peter Freyer was its first President, Lord Horder the second, Sir John Thomson-Walker the third, and Sir Walter Langdon-Brown the fourth. Since then for a period of thirty-two years without interruption the presidential chair has been occupied by a surgeon.

My main theme will be the past history of this Section and my personal recollections of some of its early Presidents. In preparation for this let me first recall some details with regard to the formation of this Section thirty-six years ago.

The Inaugural Meeting of the Section of Urology was held in this building on March 17, 1920. The President of the Royal Society of Medicine that year was Sir Humphry Rolleston. He took the chair, and eighteen Fellows and members were present, but, unfortunately, the list of names of those present has not been preserved.

The first item on the Agenda was the choice of Officers, and the following were elected:

President ..	Sir Peter Freyer
Vice-Presidents	Sir Cuthbert Wallace
	Sir Thomas Horder
Hon. Secretaries	J. W. Thomson-Walker
	Cyril A. R. Nitch

I once asked a very senior member of this Section which of the Founder Members had been the most active "behind the scenes" in promoting the formation of this Section, and he replied without a moment's hesitation "Sir John Thomson-Walker". Evidence for this is provided by the fact that at the Inaugural Meeting of the new Section he was elected the first Honorary Secretary. The President of a new Society is often only a figure-head. If you want to discover the real prime mover you must notice who gets elected as its first Secretary!

Only one of the original officers of this Section is still alive, Mr. Cyril Nitch, now living in retirement at Yeovil in Somerset. There are only three surviving "original members", distinguished in our official list by the letters "O.M.", namely, Lord Webb-Johnson, Mr. J. B. Macalpine, and Mr. Ogier Ward.

Apart from these original members, the most senior ordinary members of the Section at the present time are Sir Zachary Cope, Mr. Clifford Morson and Mr. Kenneth Walker, all of whom were admitted in 1920.

If a prize were awarded to the member of this Section who had held office longest it would, without a doubt, go to Mr. Clifford Morson, whose record is as follows: Joined the Section in 1920, elected Representative on Library Committee 1924, Secretary 1925–1927, Vice-President 1927–1931, Representative on Editorial Committee 1932, President 1933, Representative on Editorial Committee once more in 1935, an office which he has held continuously ever since. He has been a member of the Council for thirty of the thirty-six years of the Section's existence.

FIRST PRESIDENTS OF SECTION

Anyone elected to the office of President in a Society such as this during its early formative years is bound to leave his mark on the organization over which he presides, and the first four Presidents of this Section certainly did so. It is my impression now that each of these was what Emerson would have called a "representative man", and that each, perhaps unconsciously, made a unique contribution to the life of this Section. All four were men of exceptional ability and held in the highest esteem by their colleagues. Though they varied greatly in character and attainments, they were united by a common interest in urology.

SIR PETER FREYER

The first President of this Section was Sir Peter Freyer, who was then 69 years of age and at the height of his fame and professional reputation. It was twenty-four years since, on his return from India, he had been appointed to the staff of St. Peter's Hospital, and just twenty years since he had carried out the first successful suprapubic prostatectomy operation one dark December day in 1900.

I am able to show you photographs of pathological specimens derived from Freyer's first prostatectomy case, and also photographs of the patient's notes but since this is the first time this information has been made public, I must first relate how it was obtained.

I must begin by explaining that soon after my appointment as pathologist to St. Peter's Hospital in 1930, I was given custody of the Freyer Collection of Prostates, which for some years had been stored in a cupboard below a book-case in the Board Room. In this cupboard there were also a few other precious trophies and a drawer containing some 20 or 30 urinary calculi reserved for postgraduate lectures.

I consulted with Mr. Swift Joly, and when we began to sort out the Freyer Collection of Prostates we found a big jar containing a post-mortem specimen of a bladder, prostate and urethra, to which was attached a label marked with the initials "J. T." "Ah", said Mr. Joly with obvious delight, "John Thomas, the first patient on whom Freyer did his prostatectomy operation thirty years ago."

Mr. Joly explained that the patient had survived the operation for more than twelve years, and that Sir Peter Freyer had kept in touch with him regularly during this time by promising the relatives that they should be handsomely rewarded if, after the decease of John Thomas, a post-mortem examination could be performed and the pelvic organs retrieved. Mr. Joly thought that the patient had died in St. Pancras Infirmary just before the First World War.



FIG. 1.—Sir Peter Freyer.



FIG. 2.—Organs from Freyer's first prostatectomy case.

This museum specimen marked "J. T." remained in my charge for the next twenty-six years, but I did nothing to substantiate Mr. Joly's story until a few months ago, when it occurred to me that I might search through the hospital records to discover the name and initials of the patient on whom Freyer had performed his first prostatectomy operation, to see if they corresponded with the information given me by Mr. Joly. I did so, and am much indebted to the Records Clerk of St. Peter's Hospital who eventually found the bound volume of notes of all cases under the care of Sir Peter Freyer. Therein we confirmed the fact that in the month of December 1900 a patient named John Thomas, aged 69, had been admitted for prostatic obstruction and had been treated surgically by Freyer. Here are two extracts from this patient's notes.

EXTRACT FROM PATIENT'S NOTES DATED DECEMBER 1900
OPERATION (P. J. F.) GAS AND ETHER

"Suprapubic incisions: incision into mucous membrane of bladder on to right prostatic lobe: *this shelled out quite easily*. Apparently an adenomatous growth not very hard—more elastic than doughy. Corresponding incision into mucous membrane over left lobe which was treated in the same way. This was smaller but apparently of exactly the same consistency. When the right lobe was removed and got out of the way a small median lobe was felt about the size of a marble; this was removed thirdly through the incision made for the right lobe. This also seemed to be identical in its feel and consistency with the other two. Double drain tube put in."

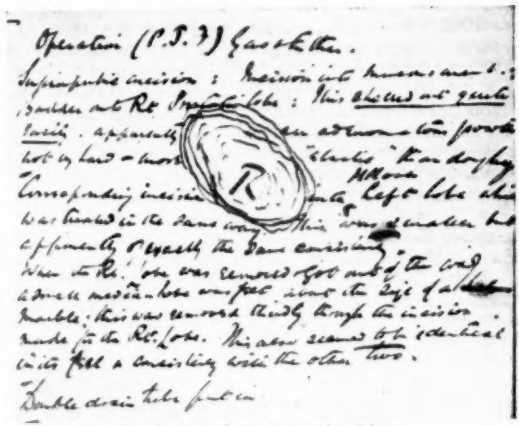


FIG. 3.—Extract from Operation Notes.

POST-OPERATION NOTES

"Passed *all* water naturally and *quite dry since three weeks and three days after operation*. Holds his water two and a half hours.

"Night two or three times.

"Had had 'gout' in ankles last week or two ago.

"April 22, 1912. Patient writes (82 years of age): 'I must say I am perfectly right in my urinary organs and for which I shall never be able to thank you enough.'

"April 1913. Died in the St. Pancras Infirmary from heart disease. The bladder and urethra preserved. (*Vide* specimen in St. Peter's Hospital.)"

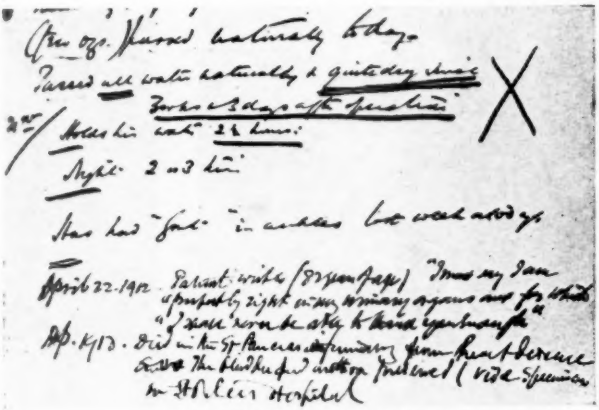


FIG. 4.—Post-operation Notes.

The sequence of events, then, in this remarkable story is as follows:

1900: Prostatectomy operation on John Thomas by Peter Freyer.

1913: Death of John Thomas: post-mortem examination and removal of pelvic organs to Freyer Collection of Prostates at St. Peter's.

1930: Discovery by Mr. Joly of organs labelled "J. T."

1956: My confirmation of Mr. Joly's story by finding notes of cases operated on by Freyer in 1900, fifty-six years previously.

There has been much controversy concerning the question whether or not Freyer was the first surgeon to carry out suprapubic prostatectomy successfully, but whatever views may be held about this, no one will deny that by his teaching and example Freyer effected a great improvement in the surgical treatment of prostatic obstruction, and it was because of his pre-eminence in this field that he was chosen as the first President of the newly-formed Section of Urology in 1920.

LORD HORDER

Sir Thomas Horder, later Lord Horder, was the second President of this Section.

I have chosen a photograph of Horder as a young man because his interest in urology began early in his career: in fact, it might be said that it was the urinary system which provided him with the key to the citadel of fame!

As a young physician he was called into consultation by the medical advisors to King Edward VII, who was thought to have sugar in his urine. Horder found that the diagnosis of glycosuria was incorrect. Above the bed of the royal patient he had noticed a number of bottles of patent medicines, and among them a popular remedy against rheumatism containing ingredients which he knew might give rise to a false positive reaction if the urine were tested for sugar by Fehling's method, then in general use. His Majesty King Edward VII was advised to abstain for a time from his patent medicines and the reducing substance in his urine promptly disappeared.

In the early nineteen twenties Horder was one of a small group of physicians who attended the meetings of this Section regularly and took an active part in its discussions. He was the second member of the Section to contribute a paper to the "Proceedings".

Horder's attendance at our meetings, and especially his presence in the Presidential Chair, provided an invaluable link with general medicine. In my view this was his special contribution to the developing life of our Section. Later on Horder became interested in so many movements, institutions and organizations that his early contacts with urology came to be overlooked, a fact on which Mr. Clifford Morson commented in a letter referring to Horder's obituary notice in the *British Medical Journal* (August 20, 1955). Mr. Morson mentioned Horder's share in the foundation of this Section, and added that even before this Section was formed Horder had expressed the view that the trend of development of urology would not be exclusively surgical.

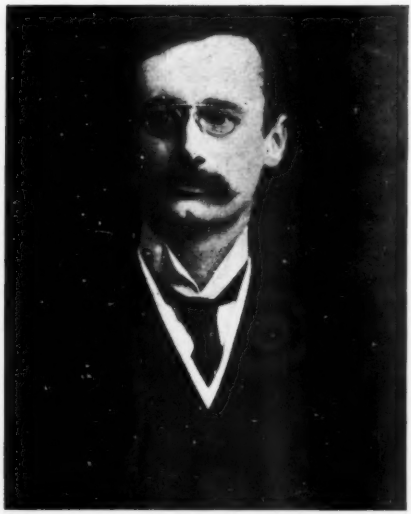


FIG. 5.—Lord Horder (as Sir Thomas Horder).



FIG. 6.—Sir John Thomson-Walker.

SIR JOHN THOMSON-WALKER

Sir John Thomson-Walker was the third President of the Section.

After the death of Sir Peter Freyer in 1921, Thomson-Walker occupied a position of undisputed supremacy in the world of urology for more than fifteen years. This was due, not to any high degree of originality in his scientific or clinical work, but to the fact that he improved and perfected the conceptions of his predecessors, and seemed to introduce a quality of excellence into all that he said or did.

I welcome the opportunity of recalling my impressions of Thomson-Walker because a year or two ago a urological surgeon at one of the big London teaching hospitals told me that he had referred to him in a lecture and found that even the registrars and assistants seemed to know very little about him. Yet it is less than twenty years since he died, and in his day his reputation was literally world-wide.

Sir John Thomson-Walker, both in dress and manner, was always "the perfect gentleman". He was tall and carried himself well. He was an upright man in every sense of the word. He was self-confident without being proud. He was well aware of his authoritative position but not in any way self-assertive. I remember a conversation during which reference was made by a patient to the leading urological surgeon of the day in the United States. Thomson-Walker remarked at once: "Of course I know him well: he is my opposite number in America." It sounded as if the King of the Old World were paying homage to the King of the New World!

Finally I must mention his industry and scholarship. I once asked him how he had managed in the midst of such a busy life to find time to keep himself up to date in pathology and other scientific subjects. He replied quite simply that his health had not been good and that he had not slept well at night, so had made a habit of doing an hour or two's study each morning before breakfast.

Sir Walter Langdon-Brown

Dr. Langdon-Brown, later to become Sir Walter Langdon-Brown, and Regius Professor of Medicine in the University of Cambridge, was the fourth President of this Section.

Langdon-Brown's presidency forged an invaluable link with scientific medicine and especially physiology.

The breadth of his vision and the variety of his interests is shown by the fact that he was elected President at different times of no less than four Sections of the Royal Society of Medicine, namely Urology, Therapeutics, History of Medicine and Endocrinology.

I met him first in 1929 in preparation for a combined discussion on urinary antiseptics between the Sections of Urology and Pathology. He was deputed to speak for the Section of Urology and I had been appointed in a similar way by the Section of Pathology. A few weeks before this meeting he invited me round one evening to his house in Cavendish Square so that we might agree on procedure. Naturally I was anxious to find out what he was going to say, and it transpired that he had the same attitude to me. But we soon came to terms. We both agreed that urinary antiseptics did no good anyhow! This, of course, was long before the days of sulphonamides or antibiotics: even before the days of the ketogenic diet.

After this I met Sir Walter Langdon-Brown on many occasions and came to know him well and to respect him greatly. He was a charming host with a great knowledge of good food and good wine, and a vast fund of anecdotes.

Phase of Restriction of Membership to Urological Surgeons

Sir Walter Langdon-Brown was President of this Section in the session 1923–24 and he was followed in succession by Mr. Cyril Nitch, Mr. Jocelyn Swan, Sir Girling Ball, Mr. Frank Kidd and Mr. Swift Joly. My impression is that during this period the control of the Section passed almost completely into the hands of urological surgeons.

It was, of course, natural that at this time most of the active members of this Section should have been surgeons, because it is they who have developed this specialty and added to our knowledge of the subject; but if you recall what I said about the first officers and early Presidents you will realize that the founders of this Section had a broader conception of the general scope of urology and at first, chiefly owing to the influence of Horder and Langdon-Brown, the medical aspects of urology were kept well to the fore. The attendance book shows that for the first four or five years of our existence a strong group of consulting physicians and a few pathologists attended the meetings of this Section regularly. Then we passed into a phase when the activities of this Section appeared to be of interest only to urological surgeons: others ceased to attend.

The gradual restriction of active membership of this Section to urological surgeons continued for a period of about twenty years, during which time physicians, radiologists and pathologists rarely attended our meetings. I can remember when it seemed almost as if *I* were enjoying an unopposed practice in pathology within this Section, a state of affairs which was neither good for me nor for the Section! However during the last three or four years this has gradually been put right and we now have a strong group of younger pathologists taking an active share in the life of the Section, especially at the clinico-pathological meetings.

Looking forward into the future, I venture to predict that the programme arranged for this Section in the coming session is likely to attract a more varied audience than in the past, and that it is not unlikely that an increasing number of physicians and even general practitioners may begin to return to the fold.

The reason why I anticipate a "come-back" of physicians is because some recent advances in urology have led to the discovery of hitherto undeveloped territories in medical know-

ledge where many others besides urologists may wish to stake out a claim. A good example is provided by cancer research. I will illustrate this by a recent personal experience.

A few weeks ago I had to travel to Italy to attend a committee meeting of the International Union against Cancer, at which representatives were present from thirty or forty different countries. We were a miscellaneous collection including University professors, whole-time research workers, clinicians, pathologists and administrators. We met in the new science buildings of the ancient university of Rome. The weather was very hot, the agenda was long, and we made slow progress. Towards the end of the third day my thoughts began to wander, and as I gazed absentmindedly at the distinguished company seated round the enormous table I began to ask myself which member of this international committee had contributed most to the advancement of our knowledge of cancer during the last few years. This was not a difficult question to answer. My eye fell at once on a member of the delegation from the United States, a surgeon known to most of you, a urologist, Charles Huggins. His researches into the pathology and treatment of cancer of the prostate are amongst the most outstanding contributions to the cancer problem made in recent years, and, as you know, they already have far-reaching implications in relation to general medicine and especially endocrinology; and we owe all this to a practising urological surgeon.

It is obvious that if discoveries such as these concerning the hormone control of cancer are being made by urologists, then it will not be long before the programme of the Section of Urology will be scanned with renewed interest by members of other Sections of this learned Society. For this reason we should be prepared for visitors and be ready to receive them.

Subsequent Presidents

Following Sir Walter Langdon-Brown there have been thirty-two Presidents of this Section, all of them surgeons.

I wish I could say something about each of the remaining deceased Presidents, because I am sure that in his day each one made his own special contribution to the life of this Section. But I have time only to speak of two more, and have chosen Mr. J. Swift Joly and Sir Henry Wade. I do not suggest for a moment that these did more than others. I chose them chiefly because I knew them both intimately and also because one, Swift Joly, was a pure urologist, whereas Henry Wade was a general surgeon with a special interest in urology.

Mr. J. Swift Joly

Mr. J. Swift Joly was the ninth President of this Section.

Swift Joly will always be remembered chiefly because of his researches into the pathology of calculus disease of the urinary tract. This was the subject of his Presidential Address to this Section and the theme of his monumental work "Stone and Calculus Disease of the Urinary Organs", published in 1929.

After his appointment to the Staff of St. Peter's, Joly confined his practice exclusively to urological surgery, but he had an immense store of learning in all sorts of subjects, was an entertaining conversationalist and possessed a quick Irish wit.

Swift Joly accomplished a great deal but was never in a hurry. One of his peculiar mannerisms was always to sign his letters "Yours in haste", which was perhaps in keeping with his name "Swift" Joly though not in keeping with his behaviour: in fact, if one met him anywhere he always seemed to have time for a leisurely chat. He loved a joke, especially if there was something a trifle whimsical or quixotic about it.

I have already mentioned that when I was appointed Pathologist to St. Peter's Hospital I found a collection of urinary calculi which were used for lectures to post-graduate students. Swift Joly knew more about these than anyone else, so I asked him to select those which he thought should be analysed chemically. Amongst the collection was a peculiar brownish oval stone about two inches in diameter which Joly said had been used for many years for teaching purposes but he knew nothing about its origin, though he assumed it was a vesical calculus. "This stone", he said, "must certainly be preserved", so I made a preliminary analysis of scrapings from the surface, and was surprised to find that these did not show the presence of any oxalates, uric acid, urates, cystin, phosphates or carbonates. Swift Joly also was much mystified by this, so we decided to bisect the stone and to submit one-half to an expert for complete chemical identification. I ought at this point to mention that when the stone was bisected we both noticed that its structure was uniform throughout and that there was no obvious nucleus or lamination and there were no concentric rings. Therefore, we were not surprised when a few days later the report arrived to say that this was not a urinary calculus but simply a big lump of plaster of Paris, thinly coated with varnish. It is still in the Museum of St. Peter's Hospital, now labelled "alleged calculus".

SIR HENRY WADE

Sir Henry Wade occupied the Presidential Chair in the session 1937–1938, and was the first urological consultant from North of the Tweed to be invited south for this purpose. He was the forerunner of other distinguished compatriots who are fortunately still with us—namely W. W. Galbraith, A. H. Jacobs and David Band.

Henry Wade was a skilful surgeon but also a very sound pathologist, and it is to this side of his character that I wish to pay my tribute both as pupil and friend.

It is now well known that operations which enucleate the prostate through its line of cleavage may result in the posterior lobe being left behind, though Sir Peter Freyer maintained at first that his operation removed the whole prostate gland. There was a good deal of controversy about this and Henry Wade became interested in the question during the two years at the beginning of his career when he worked in the Pathology Department of the Royal Infirmary at Edinburgh. It was natural therefore that when he subsequently came to London for postgraduate surgical experience he should visit St. Peter's Hospital to see for himself what Freyer was doing. He did so, and some years later in a communication to this Section he described how he had sat on a bench in the operating theatre at St. Peter's and watched Freyer swiftly and dextrously complete his prostate operation: after which Freyer brought the specimen across to where the visitors were sitting and demonstrated to his own satisfaction that he had removed the entire gland.

But Henry Wade was unconvinced.

Henry Wade returned to Edinburgh to study this question again. He cut whole sections of fifty operation specimens and made similar large slices through the prostatic bed from patients dying after prostatectomy operations. This left him in no doubt that the so-called hypertrophy of the prostate is in reality a limited hyperplasia of the more centrally placed prostatic glands. He proved that some of this may be left behind after enucleation.

Perhaps at the time it may have appeared to some as if this were an academic question only, but Henry Wade saw that it might have a bearing on the whole problem of the regeneration of prostatic tissue and on the possible site of origin of prostatic carcinoma. Looking back now into the past, to the great services rendered to this Section by my predecessors, I should like to pay my special tribute of affection to this former President hailing from North of the Tweed for his outstanding contributions both to urology and to pathology.

OTHER INFLUENCES BEHIND THE SCENES

So far in this tour "behind the scenes" I have referred only to the influence of Presidents, but I can also recall many secretaries, councillors, editorial and library representatives and others who by their loyal service helped to build up this Section to the strong position in which it is to-day. Fortunately most of them are still with us and for that reason disqualified from further mention at present.

Furthermore, to avoid any possible misunderstanding, I must explain that in this Presidential Address I have not attempted even to outline a serious history of this Section. All I have been trying to do so far is to entertain you with a gossipy sort of talk on some incidents behind the scenes, based on personal and accidental recollections.

THE UROLOGICAL PATIENT

In conclusion I am going to ask you to return to the back of the stage so that I may introduce to you a shadowy figure waiting for us unnoticed behind the scenes. This is the urological patient! I am recalling him now so that we may pay our tribute to him because it is my firm conviction that the chief incentive to the foundation of this Section was the pressing need of the urological patient. Moreover, all through the thirty-six years' history of this Section this anonymous individual has played a more important part in the development of urology than any President, Secretary, or Councillor. But for him we should not exist! In your name, as President of this Section, I now assure THE UNSEEN PATIENT that he will not be forgotten at any of our meetings, and whether our talk be grave or gay it will always be on his behalf.

We know, of course, that we come here to these meetings for many different reasons, such as to meet old friends, to enjoy each other's company and to receive instruction and edification. But deeper down, perhaps subconsciously, we come for the same reasons which inspired the Founders and original members of this Section, namely because we know that here in the fresh invigorating atmosphere of the public forum, we can discuss the urological patient objectively, without so much as a passing thought for hospital estimates or priorities or any such thing. It is a fine tradition. We have inherited this freedom from our predecessors. We must preserve it, both on the stage and behind the scenes, and hand it on unsullied to our successors.

[*November* 22, 1956]

THE following cases and specimens were shown:

Tuberculous Sinus following Nephrectomy.—Mr. E. W. RICHES.

Kidney with Double Pelvis Removed Ten Years after Transplantation of its Duplicated Ureters, Because of Hydronephrosis in Upper Segment.—Mr. ARTHUR JACOBS.

Caseous Tuberculosis in one Half of a Horseshoe Kidney.—Mr. J. H. CARVER.

Nephrocalcinosis. ? Rein-en-Éponge.—Mr. D. INNES WILLIAMS.

Granuloma of Kidney.—Mr. D. INNES WILLIAMS and Dr. R. C. B. PUGH.

Long-standing Vena Caval Obstruction and Hypernephroma.—Mr. J. C. ANGELL (for Mr. J. D. FERGUSSON).

A Fluid Renal Opacity.—Mr. MARCO CAINE.

Vesicocolic Fistula due to Diverticulitis.—Mr. N. SLADE (for Mr. ASHTON MILLER).

Bladder Stone with Glass Nucleus.—Mr. ALEX E. ROCHE.

Torsion Testis.—Mr. N. SLADE (for Mr. A. WILFRID ADAMS).

Tumour of Testicle—for Diagnosis.—Mr. DAVID WALLACE.

Carcinoma of the Urethra, Two Cases.—Mr. C. WIGGISHOFF (for Mr. A. W. BADENOCH).

Ectopic Ureter Draining into Vagina with Hypoplasia of Corresponding Kidney.—Mr. A. G. ELLERKER.

[*January* 24, 1957]

Ten-year Follow-up of Cases of Adenocarcinoma of the Kidney

By A. C. THACKRAY, M.A., M.D.

ABOUT ten years ago Mr. Griffiths and I analysed a series of cases of carcinoma of the kidney which had been seen at the Middlesex Hospital and associated wartime Sector hospitals during the preceding thirteen years (Griffiths and Thackray, 1949). We excluded from our series the transitional and squamous cell carcinomas arising in the renal pelvis and calyces, and carcinoma of the kidney as used here refers only to tumours arising from the renal tubules. The survival figures, as far as we could estimate them at that time, were as shown in Table I. We were agreeably surprised by these figures, the percentages surviving

TABLE I.—SURVIVAL RATE OF NEPHRECTOMY CASES

	Years since nephrectomy			
	One	Three	Five	Ten
Number surviving	44	24	16	4
Possible survivors	57	43	34	19
Percentage surviving	77	56	47	21

TABLE II.—PERCENTAGE SURVIVING

	Years since nephrectomy			
	One	Three	Five	Ten
Preliminary figures	72	58	48	20
Final figures ..	66	53	39	24

one, three, five and ten years being 77, 56, 47 and 21, which compare favourably with Priestley's three, five and ten year percentage survivals of 48, 38 and 27 for a large series of cases from the Mayo Clinic (Priestley, 1939). The number of survivors falls steadily from the time of operation to the ten-year limit of follow-up, with about a quarter of all patients dead within the year and about a quarter still alive at ten years. This great variation in survival time is well known; one patient may die with widespread secondaries after a few months, another may die with similar metastases after the lapse of several years, whilst occasionally apparent cures are seen. In our review of these cases we sought an explanation of these wide variations in survival and paid particular attention to any factors which we thought might influence the prognosis. We wanted to include as many cases as possible, particularly as the significance of the various factors considered had to be tested by reference to the follow-up figures, and therefore included all patients operated upon up to the time of writing. Consequently for the five-year follow-up little over half the cases were available for consideration, shown in Table I as possible survivors, and comparatively few for the ten-year figures. This survey of the ten-year follow-up series of cases is a review of the results of surgical treatment of carcinoma of the kidney. We should remind ourselves that only between two-thirds and three-quarters of all cases are in fact operated upon. Of the 80 cases in our series in which surgery was considered, only 60 were operable, an inoperability rate of 25%, quite comparable with the 28% given in the very large-scale study of these tumours at the B.A.U.S. meeting in Glasgow in 1951 (Riches, Griffiths and Thackray, 1951). Furthermore, patients are seen in the post-mortem room from time to time who have died from the effects of such carcinomas and in whom the diagnosis was never made during life.

The pathological section of our investigation was confined to those cases, 40 in number, for which microscopic sections of the tumours were available as well as the actual operation specimens or adequate descriptions of them. For this group the preliminary survival percentages are shown in Table II compared with the final percentages based on latest reports. At the time of our previous paper (1949) one or two of the cases included had been operated upon less than a year before whilst two other cases who had already survived five years could not be traced in the recent round-up and have had to be omitted from these figures. One had returned to his native Poland and we are still hoping for news of him. These changes have reduced the one-year survivals from 72% to 66%.

The pathological factors which may bear on the prognosis.—The prognosis for a patient from whom a malignant tumour has been surgically removed depends on whether the primary growth has been removed entire, on whether any metastases are already present, and, if so, how rapidly they will develop and prove fatal. From an examination of the removed tumour-bearing kidney we might hope to decide whether there was direct extension into surrounding tissues which were not removed, but it is difficult to assess this point retrospectively on the preserved specimen, and though the pathological reports may mention tumour reaching the surface of the kidney they rarely hint at whether the tumour extended to the limit of the perinephric fat removed. But from the fact of local recurrence being recorded in 9 of our 38 cases, we may take it that the primary growth is not always completely removed.

Features suggesting the likelihood of metastasis having already occurred are of obvious importance, presuming that no secondaries are clinically detectable at the time of operation. The size of the primary tumour might be expected to indicate the likelihood of metastases being present, but is, in fact, a very poor prognostic guide. Dividing these 38 tumours into equal numbers above and below the average of 3 in. diameter showed relatively little difference in survival rate. The same, incidentally, goes for the length of history. The patient who has survived the longest so far in our series, twenty years, had a three-year history and a tumour larger than the average; on the contrary, a patient who presented with paraplegia was found at post-mortem to have a circumscribed kidney tumour only 2 in. across, with no length of history as far as the urinary system was concerned, his only symptoms having been due to spine secondaries. From the size point of view the only patients who seem to do unusually well are those in whom small tumours are unexpectedly found in a kidney removed for some other condition, such as stone.

The regional lymph glands are removed together with the primary growth in operations for carcinoma in some situations such as the breast or bowel. A most important factor in the prognosis of a patient with breast cancer is whether the axillary glands are invaded. Our President's investigations into the significance of the lymphatic spread of bowel cancer are among the classics of pathology. Although the near-by lymph nodes may well be invaded in renal cancer they are not systematically removed. They were noted as involved and samples were sectioned in 6 of our cases, to which reference will be made later, but in the great majority of cases there was no mention of their condition and no conclusions can be drawn as to their significance in prognosis.

The renal tubules from which our tumours arise depend for their normal function on a copious blood supply, and the corresponding tumours seem to induce the formation of numerous and large vascular channels as they grow. The growth often invades these vascular sinuses and extends along them towards the main renal vein, eventually filling, blocking and distending it. The invading growth, often with a good deal of adherent thrombus, may extend out into the vena cava and may obstruct that vessel. Portions of the mass are liable to break off and lead to pulmonary embolism, sometimes during nephrectomy. The presence of tumour within the renal vein adversely affects the prognosis as shown in Table III. Note that despite invasion of the renal vein some cases still survive

TABLE III.—PERCENTAGE SURVIVING

	Years since nephrectomy			
	One	Three	Five	Ten
Vein free 63% ..	79	62	46	33
Vein invaded 37%	43	36	14	7

TABLE IV.—PERCENTAGE SURVIVING

	Years since nephrectomy			
Grade	One	Three	Five	Ten
I	100	92	75	42
II	66	40	27	20
III	27	27	9	9

five and even ten years. Where there was no mention of the state of the vein in the notes it was counted as free, so that the 37% incidence of renal invasion is a minimal figure.

Histological assessment of malignancy.

From the renal tubules two common types of tumour arise. Firstly, the well-known "hypernephroma" with its characteristic naked-eye appearance—golden areas and areas

of hæmorrhage—is composed of cells which are arranged in some semblance of tubules, the cells themselves being characteristically clear in the ordinary histological section since the lipoid and glycogen which they contain during life is dissolved out in the preparation of a paraffin section. This type is sometimes known as a clear cell carcinoma.

The second type is a papillary cystadenocarcinoma, which is composed of numerous cysts packed with cauliflower-like processes projecting from their walls. Though papillary in arrangement this tumour is unrelated to, though occasionally confused with, papillary growths of the transitional epithelium of the calyces or pelvis. These two types of tumour differ somewhat in behaviour, the hypernephroma having a greater propensity for blood spread with secondaries in the lung and often bones, and the papillary cystadenocarcinoma, which sometimes presents as multiple foci in the kidney, more often involving lymph nodes and liver. Despite these differences we found no significant difference in the overall survival rates for the two types.

In our original study, undoubtedly the single pathological feature of greatest prognostic significance proved to be the histological grade of malignancy. While Mr. Griffiths was extracting details from the patients' notes I settled down with the 40 sections and graded them. In grading a tumour the following points are considered: (1) The degree of differentiation or the extent to which the tumour cells are arranged either as tubules or in papillary cystic formation, the two types of tumour just described being considered together for the purpose of grading; the better the differentiation the lower the malignancy. (2) The uniformity or otherwise of the tumour cells; the greater the variation in size and staining the higher the malignancy. (3) The frequency of mitoses and hyperchromatic nuclei, features suggesting rapid growth. Taking all these points into consideration we arranged the tumours into three grades, Grade I tumours of low malignancy, Grade II of average and Grade III of high malignancy. There is no hard and fast dividing line between the grades which merge imperceptibly into one another, and there is no reason why we should choose three grades rather than four or two except convenience. The other point to stress is that the grade is a feature of the microscopic appearance of the tumour and no other factors such as size or presence of metastases are taken into consideration when grading.

Having graded our 40 tumours we correlated them with the follow-up details and found a quite satisfactory degree of agreement. Now that the cases, or 38 of them, have been followed up for the ten-year period the actual percentages have altered a little but the agreement remains good (Table IV). The percentage surviving falls steadily through the years in each grade and also falls steadily from Grade I to Grade III in each year. Of the group of 11 Grade III cases only 3 survived one year and there were no deaths between one and three years; one of the 11 survived five years and was still alive at ten years.

It is probably easier to picture the fate of these various patients by recording their years of post-operative survival (Fig. 1). The years after operation are marked out along the bottom, and lines, each representing a patient, run varying distances towards the right, corresponding to the number of years survived. With the exception of the 9 patients still alive at ten years the lifelines are terminated by a short vertical stroke indicating death. The area of black representing the sum of the years lived by the Grade I cases is strikingly larger than the black area for the Grade III cases, with the Grade II area of intermediate size. The survivors at ten years are 1 Grade III, 3 Grade II and 5 Grade I. Down the left side are a series of discs opposite the patients whose renal veins were invaded by tumour. There are only 3 of these in Grade I, 5 in Grade II and 6 in Grade III. Notice that the survival of the 3 Grade I cases with venous involvement, three, seven and over ten years, is considerably longer on the average than the Grade III vein-free cases.

The Grade III tumours grow quickly, invade the vein and infiltrate the surroundings, sometimes with quite short histories. With rare exceptions metastasis has occurred and secondaries are developing, even with quite small primaries, by the time they are operated upon. Death usually occurs within a year or two. At the very bottom of Fig. 1 we have a line reaching to the limit, a woman who had an undoubtedly Grade III tumour removed fifteen years ago and is alive and well to-day, without the help of radiotherapy before or after the operation. Either the tumour was removed before metastasis had occurred or she had well developed those powers of resistance to malignant tumour cells of which we know little or nothing. 3 of the Grade III cases with venous involvement also had invaded lymph nodes present, and of that trio the longest survival was six months.

The Grade II cases of average malignancy are more variable. 3 lived to ten years and 2, both with veins invaded, died within a week or two of operation. One of these was an old lady, then aged 70, who was strongly suspected of having a renal tumour but was not thought fit for operation. She returned seven years later with clot retention. This time her kidney tumour was removed but she died of coronary disease a week later.

The lines for the Grade I patients all extend at least two years, even those with venous involvement. Among them is a case where many invaded lymph nodes were seen when the

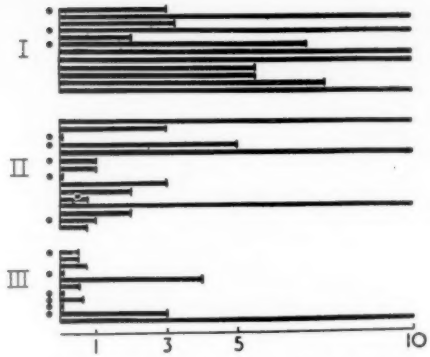


FIG. 1.—Post-operative survival in years.

kidney was removed, one being taken for section. Without further treatment she lived seven and a half years. Seeing how many of these Grade I lines reach to the ten-year limit and having seen how very regular was the histological appearance of some of the examples I showed you earlier, you may be forgiven for suspecting that the good results in Grade I are due to my having mixed in a number of simple adenomas with the low-grade carcinomas. I will admit that one of these cases was originally diagnosed as an adenoma, the shortest of the lines, for she died two years later from secondaries. The tumour was very large, measuring 8 in. × 7 in. × 3 in., so there may have been more malignant areas present. It is a rare type not corresponding to either of the two common types I mentioned; the tubules are very reminiscent of collecting tubules.

To counteract any tendency to suspect that there are some adenomas in the Grade I group, I have gone outside the limits of my title. This time the follow-up has been extended to fifteen years, and 3 of the ten-year survivors have died of recurrence at 14 years (Fig. 2).

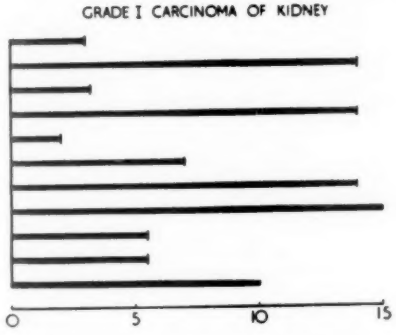


FIG. 2.—Post-operative survival in years.

One of these was a patient of Sir Gordon Gordon-Taylor's who had such striking invasion of the renal vein that a painting of the specimen was done. In these 3 cases it was noticeable that the eventual development of the metastases, which must have been present all along, corresponded with the onset of other forms of ill-health possibly lowering the powers of resistance; in one case genito-urinary tuberculosis, in another hypertensive heart failure.

Only 2 of this group of low-grade tumours are still living; one at a mere ten years and the other at twenty years. She had been troubled by a lump in her side for three years; the X-ray suggested a calcified mesenteric cyst but it proved to be a renal tumour. She has survived twenty years. Perhaps it was an adenoma. But we must be patient. At our last meeting a man was mentioned who at the age of 55 in 1929 had had a kidney tumour removed by Sir Gordon Gordon-Taylor after six months' hæmaturia. He next appeared many years later at St. Bartholomew's with a large solitary secondary in his clavicle, which was removed, twenty-four years after the original nephrectomy, when he was 79 years of age.

Grade I tumours, then, are slow growing, more or less circumscribed with no great tendency to massive invasion of the vein. Symptoms quite often are of long duration and tumours large when removed. They have nearly always metastasized, but the secondaries develop slowly and patients survive several years.

Thus we set out to see whether the pathological examination of the excised tumour-bearing kidney would help in prognosis, and suggested that what was required was some indication whether metastasis had already occurred and if so how long the secondaries would take to develop and prove fatal.

It appears that metastases are, unfortunately, very often present at the time of nephrectomy, particularly if the renal vein is invaded and the tumour is of high grade; and that the time the metastases take to develop and kill depends largely on the grade of malignancy.

By taking both the state of the vein and the grade of malignancy into consideration we can divide the cases into six categories, the survival rates for the best and worst of these being contrasted in Table V. These are, of course, only very rough guides to prognosis, to which

TABLE V.—PERCENTAGE SURVIVING

	Years since nephrectomy			
	One	Three	Five	Ten
Grade I Vein free	100	87	75	50
Grade III Vein invaded	17	17	0	0

exceptions occur; we have no control, for example, over deaths from other causes, whilst in a Grade III tumour whether or not metastasis has occurred before operation will make the difference between death in a year or so and a normal span of life.

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RICHES, E. W., GRIFFITHS, I. H., and THACKRAY, A. C. (1951) *Brit. J. Urol.*, **23**, 297.

Mr. E. W. Riches said that Dr. Thackray had given the ten-year survival figures collected from all the surgeons at the Middlesex Hospital over a long period of years. On a less ambitious scale Mr. Riches had been through his own personal series in order to determine the five-year survival. Out of 60 patients there were 42 operated upon five years or more ago, and of these 22 (52%) had actually survived for five years. 17 were in Grade I with 12 survivors (71%); 16 were in Grade II with 8 survivors (50%); 9 were in Grade III with 2 survivors (22%). In the large B.A.U.S. series, reported in 1951 (Riches, Griffiths and Thackray) the 5-year survival of all cases was about 33%; and figures were given to show how the prognosis became worse as the histological grade of malignancy became higher.

Another important factor in prognosis was invasion of the renal vein by growth, and in the previous series this had occurred in 29%. There was some correlation between histological grade and vein invasion for the vein was involved in 19% of Grade I cases, 28% of Grade II, and 48% of Grade III. In his own series the vein was involved in 15 out of 60 cases (25%). Of the possible five-year survivors 15 had involvement of the vein, and only 5 actually lived for five years.

There were bound to be anomalies in any attempt to assess prognosis, and it was only possible to give a general idea of what might happen to any particular patient; for example there was one man of 60 who had a Grade III tumour with involvement of the vein and invasion of the perinephric fat, who was alive and well eight years later. There were two others with Grade II tumours and involvement of the vein who were alive and well five and ten years respectively after operation; in their cases the tumours had been fixed, and they were each given a course of X-ray therapy before operation; he felt that this had been an influence in their survival. Wells (1954) had expressed a preference for pre-operative rather than post-operative irradiation; it was in the high-grade tumours with venous involvement that X-ray treatment had its best effect, and it was a pity that the grade and the state of the vein could not be known beforehand. Pre-operative X-ray treatment should certainly be given if there was any evidence of local fixity of the tumour. There were other factors affecting prognosis apart from the general condition and age of the patient. Invasion of lymph nodes was obviously an adverse factor, but it was remarkable how well they responded to post-operative X-ray treatment in some cases. The presence of a distant metastasis was evidence that blood-borne spread had occurred, but sometimes such a secondary deposit was single and isolated and occasionally it was amenable to surgical excision with the possibility of prolonged survival. There was little doubt, however, that the histological grade was the most important single factor in prognosis.

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Professor L. N. Pyrah referred to the question of whether the grade of tumour was consistently the same in all parts of the tumour and also in the metastases; or, alternatively, if some tumours presented the microscopic picture of more than one grade? Every surgeon operating on large numbers of kidneys must have encountered the small to medium-size yellow cortical tumour which the pathologist sometimes reports as an active adenoma, or a low-grade hypernephroma, or even a latent carcinoma of the kidney.

If we accepted the fact that these cases were latent carcinomata or latent hypernephromata and included them in a series, it would weight the prognosis of the lower-grade tumours favourably; the real explanation might, however, be due to a marked difference in the biological behaviour of these latent cases from that of a definite kidney carcinoma. Was it possible to differentiate these two kinds from the pathological sections?

There was the possibility of removing isolated metastases resulting from a primary hypernephroma of the kidney, sometimes, in fact, before the primary tumour was clinically recognizable. The speaker had had one case in which the leg was amputated for a malignant growth which turned out to be a secondary to a hypernephroma; the left kidney containing the primary hypernephroma was subsequently removed and so far the patient was well. Another patient with a medium-sized hypernephroma of the right kidney was treated by nephrectomy; seven years later he was successfully operated on for a cerebral metastasis and he died after a further two years from a metastasis in the remaining kidney.

Professor D. F. Cappell asked about the foam cells shown in the papillary tumour of the renal cortex. He had seen other examples of this condition, heavily laden with foam cells and he wondered why these tumours collected foam cells within their stroma. Pathologists were interested in cholesterol in a variety of conditions. That these tumours have such striking collections of lipoid cells in the stroma might indicate that the renal cells from which one assumed they were derived had some definite function in this respect.

Secondly, he was much struck with the confirmation of what was precisely his own experience, viz. that it was impossible to give an accurate prognosis in the individual case. The tumour which was called Grade I was, on the average, more likely to have a good prognosis or to survive longer, but it was unsafe in any particular case to give a prognosis on the basis of involvement of renal veins.

Pathologists should endeavour to grade their tumours so that an accurate comparison could be made between one centre and another. Before that could be done, however, for the results to be worth-while there must be some agreed uniform standardization. Thanks to Dr. Cuthbert Dukes this had been done with bladder tumours, and there should be agreed standard criteria by which renal tumours would be graded on their histology.

Mr. Wilfrid Adams hoped a word could be said about dormancy in this sense: did we assume that a single Grawitz cell or microscopic clump, via the lung, seeded itself or was it the sole survivor of myriads? What factors in the patient explained the distinctive very late solitary metastasis of this nephroma? He wondered if Dr. Thackray could define the meaning of the old discarded term "hypernephroma".

Mr. A. W. Badenoch mentioned a male of 79 who was referred to the X-ray department at St. Bartholomew's Hospital by Mr. R. S. Murley with a large tumour in the right clavicular region which on biopsy was found to be an adenocarcinoma of the kidney. The right kidney had been removed twenty-four years before by Sir Gordon Gordon-Taylor, a retrograde pyelogram on the left kidney was quite normal.

X-ray therapy was non-effective. Mr. Murley removed the metastasis and the patient lived for ten months. This was the longest interval he knew between the removal of a renal adenocarcinoma and the development of a secondary. He had a man in his ward now who had the 11th left rib with a tumour removed at the Brompton Hospital in November 1952. Histologically the tumour was an adenocarcinoma of the kidney. On investigation a small filling defect caused by a tumour in the upper pole of the right kidney was revealed and a nephrectomy was performed in January 1953.

He remained perfectly well up to three months ago, when he developed backache due to a metastasis of the 5th lumbar vertebra, i.e. three years after removal of the secondary and primary growths.

If the spread of the tumour were assessed in conjunction with the histological grade one would arrive at a more accurate prognosis. Mr. Badenoch thought that if at operation it seemed that the whole of the tumour had not been removed, X-ray therapy should be given but prophylactic irradiation, other than to the renal fossa, did not seem practical.

Dr. Thackray, in reply, said that Professor Pyrah had asked whether the grading held good in all parts of the tumour. In a small percentage of cases there was a sharp difference in the grading in different areas of the growth; a careful look at the cut surface of the tumour might show well-defined and apparently encapsuled areas and other regions where the growth was obviously infiltrative. He had slides of tumours which were low-grade in part and elsewhere high-grade. The various grades of carcinoma merged into one another, Grade I carcinoma would merge into adenoma and the histological distinction between the two might be very difficult to make. A series of very small tumours discovered unexpectedly in kidneys removed for other reasons was being followed up. Certainly, in the literature, one or two large adenomas had been reported with the remark that the patient was well a year or two later. The report would have been of much greater value if it had waited twenty years.

He had no personal experience of secondaries being removed from the lungs and elsewhere. In reply to Professor Cappell, papillary cystic growths often had a good deal of hæmorrhage into the lumen, and the epithelial cells contained hæmosiderin. Though lipoid was often noted within the papillary processes he had no information about the mechanism by which it got there.

He agreed that it was very rash to give a definite prognosis in these cases, and could give no reason why groups of tumour cells should remain dormant in various sites for long periods. In reply to Mr. Wilfrid Adams he said that the term "hypernephroma" was much easier than "adenocarcinoma of the renal parenchyma". He hoped that they would get used to the term which Mr. Adams had suggested—"nephroma". The tumour was composed of renal epithelial cells and was comparable with hepatoma in the liver.

The Aberrant Renal Artery [*Synopsis*]

By F. T. Graves, M.S., F.R.C.S.

In 1953 the anatomy of the human intrarenal arteries was investigated in order to discover whether there was a constant pattern of these vessels. The arteries of post-mortem specimens were injected with a resin which subsequently solidified; the organic material was then removed by corrosion. The investigation showed that the distribution of the arteries within the kidney substance is constant and that upon this arterial basis the organ is divisible into five segments. It was also shown that there is no collateral circulation between these segments.

Although the initial work was done mainly as an aid to renal surgery, at the same time a study was made of the arteries of the renal pedicle, particularly those said to be "aberrant" arteries. Hitherto, a popular view has been that normally the kidney is supplied by a single renal artery which enters the hilum and that any additional artery entering the organ at one or other pole is necessarily an extra and aberrant source of supply to that provided by the main stem artery.

The investigation has included a study of more than seventy casts and sixty arteriograms. It has been found that in those cases where the main stem of the renal artery divides into the intrarenal arteries at the hilum, that is the "normal" arrangement, the artery to the lower segment frequently takes its origin from the main stem at a point more proximal than do any of the others. It was also found that when the renal pedicle consisted of more than one artery, the additional artery was one of the segmental arteries, most often to the apical or lower segments, whose origin was more proximal than usual.

The variations of the intrarenal arteries have been classified into Groups and Types (Graves, 1954, 1956):

Artery	Variations in the "normal" (division at the hilum)	Variations presenting as "aberrants": At the hilum	In the pedicle	From the aorta
Main stem	—	—	Early origin of divisions	Separate origin of divisions
Apical segment	Types 1, 2 and 4	—	Type IIIa	Types III b, c, and d
Lower segment	Type A arranged with other anterior segment arteries as in Groups 1, 2, and 3	Group 1 with long lower segment artery	Type B	Types C, D, E, and F

This table has been made for clarity and convenience. There is, in fact, no real difference between the variations of the so-called "normal kidney" and those of the apparently grossly abnormal kidney with four "aberrant" arteries. If the arteries of the renal pedicle are examined in conjunction with the intrarenal arteries and not as separate entities, then it becomes evident that the so-called aberrant or accessory arteries are really normal segmental arteries whose origin is more proximal than usual. This proximal origination accounts for many of the cases of multiple or "supernumerary" arteries of the renal pedicle.

Like the normal segments of the kidney, the segments supplied by "aberrant" arteries have no collateral circulation between their areas, so that ligation of such a vessel will result in necrosis of the area supplied.

Study of the embryology of the renal arteries as described by Felix (1912) provides an explanation for the variations of the segmental arteries. It is probable that those intrarenal arteries which have a proximal origin at the hilum or from the pedicle are the result of variation in the degeneration of the *rete arteriosum urogenitale*, whilst those which arise from the aorta are persistent mesonephric arteries.

In order to provide a clearer nomenclature, it is suggested that the "aberrant" artery in question should be given its name and type, as, for instance "The Lower Segment (aortic)

Artery," and that the words "aberrant" and "accessory" should be avoided, as they have little anatomical, surgical or descriptive value.

For further details and illustrations of "Aberrant Arteries" *see* Graves (1956).

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Mr. E. W. Riches wondered how many times Mr. Graves had seen infarction after the lower polar artery had been divided. He thought that it must occur but presumably if there was no infection it did not matter. The only relevant specimen of which he knew was that illustrated by Ball and Evans (1932) of a septic infarction following ligation of a lower polar artery. It was easy to remove a constriction at the pelvi-ureteric junction by dividing the artery which appeared to produce it, whether it was the initial cause of the hydronephrosis or only a secondary factor, and they all had patients in whom the hydronephrosis had apparently been cured in this way. Since Mr. Graves had drawn attention to the distribution of the renal arteries he had been reluctant to divide an artery to the lower pole unless he was going to remove that pole at the same time. In doing a partial nephrectomy it might be possible to cut off the blood supply of the part one wished to resect by ligating the corresponding segmental artery; this might be safe for the apical or the inferior segmental artery but not for the posterior branch which supplied a large area of the upper and middle segments.

He was a little worried over the term "aberrant" or "accessory" artery which had been in use for such a long time; perhaps it should be called an "anomalous artery". If an aberrant artery was one which had an abnormal origin or entered the kidney in an abnormal position there were very few aberrant arteries connected with hydronephrosis; more often it was the inferior segmental artery which was involved.

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Mr. H. K. Vernon said that he agreed with Mr. Riches that if a polar artery were divided, an area of infarction occurred, but it did not matter. In a case of obstruction of the ureter by a lower pole artery, it was not stressed sufficiently that the obstruction was not at the uretero-pelvic junction. The obstruction occurred a little below the pelvi-ureteric junction, and the ureter was dilated between the latter and the obstruction. He had found that simple division and ligation of the artery was sufficient to relieve the basic symptoms and, in many cases, improve the hydronephrosis.

Mr. Wilfrid Adams described a case where five separate arteries supplied a little hypoplastic kidney in a woman of 80 years. It seemed to him to corroborate Mr. Graves' explanation of the normally developed system of segmental arteries in the ordinary mature kidney.

With regard to the aberrant artery he thought it explained the hydronephrosis in a substantial number of cases. There might be neuropathy in some, intrinsic pyelo-ureteric obstruction in others, but the mere division of the artery might cure. Division of the artery in a girl of 4 with a large hydronephrosis had allowed the pent-up urine to rush down the ureter, like water over a dam; it was most spectacular.

Another interesting point was the question of its influence as an end artery on the subsequent anatomy of the kidney. Certainly in this patient, twenty years later, the girl was normal and the pyelographic pattern perfectly symmetrical on the two sides! Was it really a terminal artery? Mr. Graves might have an explanation in the arteriolar network of Felix; if that were so, surely there would be dilatation of some of the tributaries. Mr. Graves did not say whether by his solvent there might be breaking off of the ulterior branches, in which case some of the network of the anastomosis might have preserved the lower pole thus explaining why there was no corresponding atrophy. It might also explain those cases of partial nephrectomy where ligation of the inferior segmental artery was still followed by bleeding which did not seem to harmonize with the segmental distribution which Mr. Graves had mentioned.

Mr. Toby Levitt referred to the associated distribution of the gonadal and adrenal vessels which were shown to be derived from the renal artery. He wondered whether Mr. Graves had had the opportunity of studying the co-ordination between the adrenal and gonadal complexes and the renal complex? It would be interesting from the surgical angle if he could institute an inquiry into the proportion of the blood supplied by the renal pedicle to the adrenals and the gonads.

A practical point was to what extent, in carrying out a nephrectomy, these rather important and useful structures were damaged. Could it be that nature in duplicating these organs had anticipated the possibility of surgical or other intervention?

Dr. C. G. Whiteside said that he had had some suspicion that the aberrant vessel was part of the normal tree. In the angiographic literature it was pointed out that where the renal pelvis was divided or doubled, an aberrant artery was very common. At the beginning of his series he thought it was true that a large number of cases of divided pelvis or double pelvis appeared to show aberrant arteries. From recent studies, however, he had had doubt about this because he had had several cases of double pelvis with only a single artery.

Mr. Graves, replying to the discussion, said that he would like to make two points clear. First, that the work which he had described had been done entirely in the laboratory; the facts could be checked by examination of the casts (a number of casts were demonstrated at the meeting) and the arteriograms which had been made to supplement and confirm the evidence obtained from the casts. Secondly, his paper was concerned only with the anatomy of the aberrant renal arteries, and he had not intended to raise or discuss the subject of hydronephrosis.

From the evidence produced by his experimental work, he was sure that if a segmental artery was ligated or divided then the area supplied by that artery would become ischæmic. He felt that it was unwise to leave ischæmic tissue present in the body and particularly in the kidney.

A surgeon had once told him that on one occasion when he had compressed a segmental artery at operation the area of the kidney involved had not changed colour as was usual, and he had asked for a possible explanation. Mr. Graves had suggested that this failure to change colour might be due to one of three causes: either the surgeon had not compressed the vessel for long enough or had compressed it incompletely; or, the lack of cyanosis might be due to a high oxygen content of the venous blood in the area. In the latter case, the venous blood in the area would continue to circulate to some extent, even after compression of the segmental artery, because unlike the arterial system, there was no segmental arrangement of the intrarenal veins which had a free anastomosis throughout the entire kidney. This free anastomosis probably accounted for the bleeding from the cut surface of the kidney which had been noted by Mr. Wilfrid Adams, after ligation of the segmental artery.

Mr. Graves then defended his own suggestion that the name "aberrant" should be avoided. The names "aberrant" and "accessory" were so often used loosely and implied an extra blood supply, which was not present. The word "aberrant" meant "*wandering from its normal course*". Scientifically this was not applicable as the artery was a normal segmental vessel which had retained its embryonic origin and furthermore, rather than being a vessel which had grown out abnormally, was a mesonephric artery which had not faded away. Finally, if an artery was in fact the lower segment artery, why not say so? It would make for a clearer understanding in publications and discussions.

In answer to Dr. Whiteside's question, Mr. Graves said that he had had no specimens in which the pelvis or ureter had been duplicated. He was at the moment trying to collect material to study the blood supply in cases such as these.

In answer to a Member's question, he said that the blood supply to the renal pelvis had been described by Douville and Hollinshead (1955).

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[*March* 28, 1957]

THE following cases and specimens were shown:

Retroperitoneal Fibrosis.—Dr. ANN MILES THOMAS (introduced by Mr. I. H. GRIFFITHS).

Hypernephroma with Metastasis in Right Talus, Treated by Nephrectomy and Right Below-knee Amputation. 7 Year Follow-Up.—Mr. T. M. ROBINSON (for Mr. M. F. NICHOLLS).

Phæochromocytoma with Areas of Calcification.—Mr. J. H. CARVER.

Two Cases of Ectopic Ureters.—Mr. J. P. MITCHELL.

Retrocaval Ureter.—Mr. J. A. LOEB.

Osteomalacia following Ureterosigmoidostomy.—Dr. A. R. HARRISON.

Bilateral Seminoma.—Dr. R. C. B. PUGH.

Open Operation for Bladder Neck Stenosis. (a) Cystogram. (b) Cine Micturating Cystogram.—Mr. J. HOPEWELL.

Two Cases of Appendiculo-vesical Fistula.—Mr. J. D. HENNESSEY.

Vesico-cœlomic Drainage for Ascites.—Mr. D. K. MULVANY.

Section of Physical Medicine

President—A. C. BOYLE, M.D., M.R.C.P.

[*January* 9, 1957]

DISCUSSION ON GENERALIZED ACHES AND PAINS FROM METABOLIC BONE DISEASE

Dr. G. Alan Rose (University College Hospital): *Bone Pains in Steatorrhœa*

That a connexion exists between steatorrhœa and osteomalacia has been clear since the work of Parsons (1927) and of Bennett *et al.* (1932). In dealing with the individual patient, it may be obvious on clinical grounds that the patient is suffering from both of these conditions. Thus, he may present with the frequent, foul, frothy, offensive and bulky stools characteristic of steatorrhœa, and with gross bony deformities, and with tetany. In such a case the diagnosis will be easy, and is readily confirmed by biochemical and radiological investigations. The state of affairs may, however, be entirely different. The stools may have few or none of the characteristics mentioned. L. D., a patient recently described as "Case II" of Davies *et al.* (1956), had probably had steatorrhœa for very many years. She habitually used purgatives to obtain adequate bowel actions, and had never suffered from diarrhœa. This constipation may have been partly due in more recent years to a hypercalcæmia caused by a parathyroid adenoma, but this could not have been the whole explanation. V. M., a woman of 35, was found to have steatorrhœa at a time when she was having a bowel action once every three days. During the next ten years she developed frank diarrhœa, and finally osteomalacia. If the patient has a low intelligence quotient a history of diarrhœa may not be readily obtained. Patient L. B. was a girl of 17 when the diagnosis was made of steatorrhœa due to cœliac disease, with rickets and dwarfism. She had suffered from recurrent and severe attacks of diarrhœa from the age of 6 months; neither she nor her mother, however, worried much about these attacks, and her complaint on admission was that her knees were painful from banging one against the other (she had knock-knees). A patient with such an I.Q. may not appreciate the pallor of the stools, even if this is obvious to the doctor. Patient V. M. discovered by experience that a low fat diet tended to reduce her diarrhœa, when this finally developed. Others may find by trial and error that a low gluten diet helps them. Thus for various reasons, steatorrhœa may be present but not recognized.

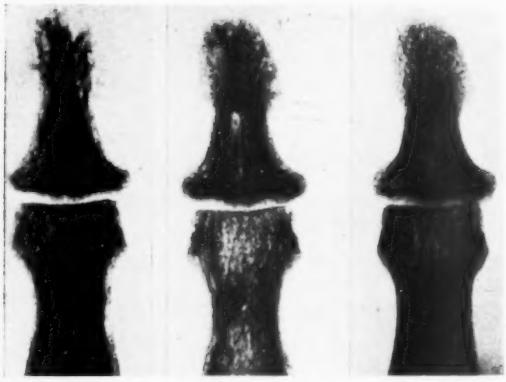
The precise time relationships between the onset of steatorrhœa, and the onset of osteomalacia are not clear. Our present concept is that the steatorrhœa develops first, and is occult or overt. After a period of time, which is variable, but of the order of three to ten years, osteomalacia may develop. When this occurs, the steatorrhœa may still be occult. The onset of osteomalacia may be fairly sudden or it may be insidious. It is therefore possible that a patient with steatorrhœa may present only with the symptoms, either early or advanced, of osteomalacia. We may therefore hazard a guess that amongst the mass of patients presenting with general aches and pains, there will be some who are developing this syndrome. It is important to try and pick out these patients before they have developed crippling deformities, since therapy can prevent the deformities from occurring as well as curing the pains and other disabilities which precede them.

In our experience, patients with early osteomalacia due to steatorrhœa may often present with a certain pattern of symptoms whereby they may be recognized. The pains usually start in the lower half of the body, in the legs, thighs, pelvis or back. They are not sciatic in distribution and are frequently bilateral. The patient can usually clearly indicate that limb pains are between joints, and not in the joints themselves. After a period of time, the pains spread to other bones of the body, affecting the arms and shoulders. The bones may be tender to the touch. F. D., a woman of 58, had steatorrhœa with osteomalacia. The

lightest tap on her skull, long bones or thoracic cage caused her to wince. This may well suggest the diagnosis of "hysteria", but it should also suggest possible metabolic bone disease. The lower ribs may be tender. This was so in patients F. D., S. G., and M. Each of these patients stated that, on turning over in bed at night, she experienced pains in the lower ribs and in other bones. This was sufficiently distressing to make them arrange their bedding in ways calculated to prevent movements in their sleep. Muscular weakness is a feature frequently alluded to in various ways. A patient may develop a waddling gait, and this may be the first symptom recognized by him, or by his friends or relatives. Patient A. B., a woman with occult steatorrhœa, developed severe muscular weakness of the legs,



FIG. 1.—Radiograph of pelvis of a woman with steatorrhœa and osteomalacia of sudden onset, and with tetany. The bones are almost normal in shape, but show Looser zones in the pubic rami.



A B C

FIG. 2.



FIG. 3.

FIG. 2.—Radiographs of phalanges of a single finger of "Case II" of Davies, Dent and Willcox (1956). The patient had steatorrhœa and two parathyroid adenomata. A, before treatment (January 3, 1955) showing subperiosteal erosions. B, February 3, 1956, two months after removal of second adenoma. C, December 1956. The bones are now normal. This last follow-up radiograph was made after the paper of Davies, Dent and Willcox had gone to press. The others are taken from their paper, by kind permission.

FIG. 3.—Radiograph of lumbar vertebræ of "Case I" of Davies, Dent and Willcox (1956), reproduced by kind permission. Each vertebra is biconcave and shows two horizontal zones of osteosclerosis, between which is a less dense zone. The patient had steatorrhœa and radiological signs of hyperparathyroidism in the phalanges.

so that she was obliged to go up the stairs on all fours. Other patients have experienced feelings of "stiffness" in the legs on getting up, and which wear off with exercise. Others have felt unsteady on their legs, or unsure of themselves. These symptoms are not due to pain, or deformities, or general nutrition, and are reversed by treatment with vitamin D only. The other well-known symptoms of steatorrhœa may, of course, be present. There may for instance be nocturia due to delayed excretion of a water load. There may be a sore tongue, latent or overt tetany, or œdema.

The more fortunate patient who has developed osteomalacia due to steatorrhœa will be diagnosed before deformities occur. At this stage there may be no signs of old rickets, and the X-rays of the skeleton may appear entirely normal. Nevertheless, the diagnosis, when suspected, may be confirmed by a few simple tests. The urine calcium may be easily assessed in an out-patient department by the Sulkowitch test on any reasonably concentrated specimen of urine. The twenty-four-hour urine calcium provides the same information in a more precise manner. In the presence of normal renal function a very low urine calcium is suggestive of steatorrhœa. This may be so even if the plasma calcium is normal or high. Biochemical osteomalacia is demonstrated by the combination of a low plasma calcium and/or a low plasma phosphorus, with a raised plasma alkaline phosphatase. The diagnosis of steatorrhœa is confirmed by inspection of stools, by fat balance, glucose tolerance curve, water excretion test, blood count, and other tests.

In the less fortunate patient, there will be advanced bone changes before the diagnosis is made. These changes follow along certain now well-defined lines. If the osteomalacia is of relatively sudden onset, it will be characterized by the development of pseudofractures or "Umbauzonen" of Looser (1920). These zones of decalcification are considered by Dent and Hodson (1954) to occur in any relatively acute osteomalacia. Fig. 1 shows such pseudofractures in the otherwise apparently normal pelvis of a woman with steatorrhœa. If the osteomalacia is of more gradual onset, as has occurred in most of our cases, then the characteristic deformities of the chest, pelvis and legs will develop. Clinically relative trunk shortening will be found and X-rays will show that the bones are rarefied. The clavicle will droop, the tri-radiate pelvis will be seen, and there may be marked coxa vara. The X-rays of the lateral spine will show the biconcave "cod-fish" vertebræ, plus signs of decalcification. Each vertebra will have collapsed to the same extent as its neighbours. The osteomalacia of steatorrhœa may, as can occur in renal failure, be accompanied by radiological signs of secondary hyperparathyroidism. This has been described recently by Davies *et al.* (1956). One such sign is the "rugger-jersey spine" in which there are horizontal bands of sclerosis and porosis in each vertebra, as can be seen in Fig. 3. The subperiosteal erosions (Pugh, 1951) may be present. Fig. 2 shows the phalanges of a single finger of "Case II" of Davies *et al.* (1956) on three separate occasions. This patient had steatorrhœa and osteomalacia; subsequently she was presumed to have developed primary hyperparathyroidism following prolonged secondary hyperparathyroidism. These X-rays show the complete reformation of bone following removal of two parathyroid adenomata and massive vitamin-D therapy.

We now have good therapy for these cases of osteomalacia. A gluten-free diet is given if the patient has been shown to be gluten-sensitive and if he will be able to continue this as an out-patient. It is supplemented with folic acid, and with a form of vitamin D, in suitable dose. At present, we use calciferol, or dihydrotachysterol, or vitamin D_3. It is our hope that it will be possible to pick out more cases of osteomalacia with occult steatorrhœa who present with generalized aches and pains before they develop deformities, in order that early treatment will prevent these deformities from ever occurring.

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Dr. F. H. Lumb (University College Hospital): *Pain in Renal Osteodystrophy*

Like steatorrhœa, chronic renal failure may be the cause underlying a variety of skeletal aches and pains which are diagnosed for long periods as fibrositis or rheumatism. It would be wrong to claim that renal osteodystrophy is a common cause of such symptoms, though this does not detract from the importance of its diagnosis. That this is so is shown by the very satisfactory response to treatment of patients with this condition, both in terms of prolongation of life, and of symptomatic relief. Once a renal cause for skeletal pain is suspected, a few simple observations and investigations go far towards establishing the

diagnosis. Furthermore, treatment other than that based on an attempt to correc the underlying biochemical disorder is of little value, failing to affect the discomfort an in-capacity, which gradually increase in severity. It would thus seem reasonable to atten t to define the main clinical characteristics of the renal osteodystrophies, as they often re nain for long unrecognized, even in patients already known to be suffering from chronic enal failure.

Various types of renal disease may be associated with bone abnormalities. In ge eral, predominantly glomerular failure, as in chronic nephritis, is associated with nit gen retention, and with raised serum phosphorus and low serum calcium levels. Bone pain may occur in such cases, and some show radiological evidence of secondary hyperparathyroidism, though not necessarily so. Tubular defects, as in the Fanconi syndrome, may also be associated with bone pain, though in these cases nitrogen retention may not be marked and the initial radiological changes are more those of osteomalacia (Albright and Reifenstein, 1948). Whatever the underlying renal disease, or type of bone change present, the symptoms tend to follow a common pattern. Also as the bony abnormality is due to biochemical disturbance and therefore generalized, it is hardly surprising that the patient's complaint should resemble those described in other forms of metabolic bone disease, as discussed by Professor Dent and Dr. Rose.

Both history and physical examination may greatly assist in the diagnosis of renal osteodystrophy. Obviously the clinical picture is greatly affected by the age of the patient, for in children chronic renal disease produces stunting of growth and deformity as its main skeletal manifestations, and such cases often present at orthopædic centres. Here, however, we are mainly concerned with adults, in whom bone pain is often the only presenting feature. Before discussing this symptom, however, another common aspect of the patients' disorder deserves mention. This concerns their previous contact with doctors and hospitals, where they have been seen on account of their increasing discomfort. In their attempts to obtain relief from pain they have often received treatment in various departments of physical medicine, orthopædics and sometimes psychiatry, not to mention general medical and other clinics. In one instance, a 35-year-old woman with a renal tubular defect and severe skeletal pain remained undiagnosed for six years, during which time she received a varied assortment of treatments which ranged from plaster casts to Evipan narcosis. The discovery of amino-aciduria in 1949, whilst she was undergoing neurological investigation, led to the diagnosis being established, and measures to correct her disturbed biochemical state have been associated with a most satisfactory symptomatic improvement. She is now in full-time employment as a shorthand typist.

In considering the case histories of those patients with renal osteodystrophy who have been under the care of Professor Dent at University College Hospital, the following features emerge. Pain, as mentioned previously, is the dominant symptom. As would be expected in a condition where the bones are generally affected, the pain is mainly referable to those parts of the skeleton which are subject to maximum stress and trauma. Thus pain affecting the lower limbs or lumbosacral region is a common complaint. It is often described as a severe, constant, nagging ache, difficult to alleviate, and of gradually increasing severity since its onset. It differs from sciatic pain in its usually bilateral distribution, and though it may be felt down the back of the thigh, it rarely spreads below the knee. Sometimes it is more definitely localized, coinciding under these circumstances with the presence of a stress fracture. Some patients notice marked bony tenderness, especially affecting the shins and ribs.

Characteristically, any increase in local stress is associated with an exacerbation of the pain. Almost always it is intensified by weight-bearing, and walking becomes more and more painful, resulting in restriction of activities and final immobility. Even the latter, however, may not give relief, as in the absence of treatment, the pain becomes more generalized, and even slight movements may become intolerable. Changing their position in bed is dreaded by some of these patients, who are wakened from their sleep by sudden movements, so much so that they not infequently go to considerable lengths to immobilize themselves by particular arrangements of pillows and bolsters. Similarly, if the ribs are affected, and stress fractures present, the patients will go to considerable lengths to suppress coughing on account of the discomfort which ensues.

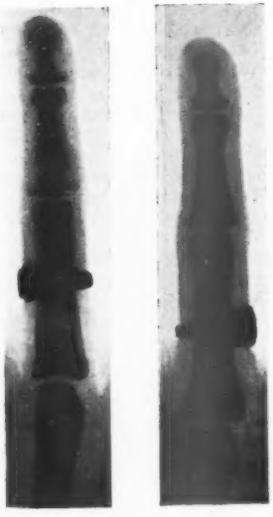
Difficulty in walking may be due to the pain described, but occasionally seems to occur in the absence of the latter, or at least before pain is severe. The patient may describe a sensation of stiffness around the hip-joints and a feeling of uncertainty when on his feet. Such symptoms are usually associated with an obvious disorder of gait, best described as a waddling gait. One patient described a sensation of stiffness in the thighs, which limited walking in the absence of actual pain. Muscular weakness is often prominent in cases of renal osteodystrophy and may be extreme. It seems to be something more that the general lassitude of chronic uræmia and associated anæmia, and is a further reason why walking

may be difficult. As is well known, in those cases where potassium loss occurs consequent on a tubular lesion, periods of actual muscular paralysis may occur.

The combination of the pain, difficulty in walking, and muscular weakness described, should raise the diagnostic possibility of a renal osteodystrophy, and indicate the lines for further enquiry. The clinical picture described may long precede the malaise, vomiting and pruritus which signalize the terminal phase of renal failure, and these manifestations should not necessarily be expected. The osmotic diuresis, which, however, occurs at an earlier stage, gives rise to polyuria, nocturia and thirst, and such symptoms are worth enquiry.



FIG. 1.—Radiograph of the pelvis, showing stress fractures in the pubic rami of a patient suffering from chronic renal failure. The fractures healed with subsequent treatment.



A B

FIG. 2.



FIG. 3.

FIG. 2.—Radiographs of a finger, A before and B after treatment, showing the subperiosteal erosions associated with secondary hyperparathyroidism, in a case of chronic renal failure.

FIG. 3.—Radiograph of the spine, from the same patient as Fig. 2, showing the increased density of the upper and lower parts of the vertebræ—the "rugger-jersey" appearance.

They are especially marked in patients with tubular defects, even though in these conditions there may be little associated nitrogen retention. Such polyuria may occasionally determine an undue persistence of enuresis.

The past history may be helpful in various ways, especially if revealing a previous illness likely to have been responsible for chronic renal impairment. Long-standing renal dysfunction, present from childhood, may have produced disturbance of growth, the patient having been left behind by his younger siblings. The family history also repays investigation—similar cases in the patient's generation may indicate a Fanconi syndrome—whilst the affection of several generations with similar symptoms directs attention to such possibilities as polycystic disease of the kidneys.

The examination of these patients may afford further information of diagnostic value. Often they show an earthy pallor, in association with an anæmia, though in some cases well-marked brownish pigmentation may be present. This appearance is especially marked where there is tubular dysfunction and electrolyte loss and the pigmentation is essentially similar to that seen in chronic adrenal insufficiency, being well marked in the skin creases, over pressure areas and sometimes affecting mucous membranes. It is of interest to note that patients with renal osteodystrophy are not usually hypertensive, the blood pressure being often normal, or even low. This is perhaps important in the genesis of their disability, as marked skeletal lesions depend for their production on a renal failure of long standing, which is more likely to occur in the absence of hypertension and its complications.

If long-standing renal impairment has been present from childhood proportional dwarfism is the rule, though in some cases surviving puberty the limbs have been described as disproportionately long in comparison with the trunk—perhaps due to inhibition of epiphyseal fusion by some factor associated with chronic renal failure. Where tubular dysfunction presents in middle age, loss of height may be apparent. Further examination may disclose other suggestive features, such as marked bone tenderness, while such features as palpable polycystic kidneys would be of obvious diagnostic importance.

With a suggestive history and corroborative signs as described, the diagnosis may be further confirmed by simple investigations. A simple examination of the urine is of first importance. A dilute urine, containing protein and perhaps glucose, greatly increases the likelihood of a renal cause for vague skeletal pain. The Sulkowitch reaction requires further interpretation in the renal cases, where calcium excretion may be lowered, as in glomerular failure, or raised, as in states where tubular function is abnormal.

Radiography may be of value, though not necessarily so, as pain from bone involvement may be present before visible X-ray changes occur. Where there are clinical grounds for suspecting renal osteodystrophy, a negative X-ray does not abolish the necessity for further biochemical investigation. This does not imply, however, that radiography may not be of the greatest assistance (Dent and Hodson, 1954). Various different bone pictures may be seen, but, in general, the tubular defects as in the Fanconi syndrome are associated with a greater or lesser degree of skeletal rarefaction, and stress fractures are of great diagnostic importance (Fig. 1). Secondary hyperparathyroidism in glomerular failure is usually associated with visible radiological change (Fig. 2) and the interesting bony sclerosis affecting various parts of the skeleton being responsible for the "rugger-jersey" spine seems to be associated with this condition (Fig. 3) (Crawford *et al.*, 1954). Sometimes the X-rays may show a combination of these various changes, as would be expected from previous pathological studies (Gilmour, 1947; Follis and Jackson, 1943; Follis, 1950).

The recognition of renal osteodystrophy in patients with suggestive symptoms mainly depends on the possibility being borne in mind. Confirmation of the diagnosis is not difficult, and is rewarded by the excellent symptomatic response which may follow such measures as large but cautious doses of vitamin D and the correction of an associated acidosis. The diagnosis deserves consideration in all cases where pain of skeletal origin is not explicable on other grounds.

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Professor C. E. Dent (University College Hospital): ***Pain in Some Metabolic Bone Diseases Not Due to Steatorrhœa or Renal Failure***

Before describing further types of adult bone disease, I will review briefly our general experience of all types at University College Hospital during the last five years. During this period our metabolic ward has been functioning and nearly all the cases I will mention have been admitted there and have been very thoroughly investigated. This data is summarized in Table I. It will be seen that, apart from steatorrhœa and the various forms of renal

TABLE I.—CASES OF METABOLIC BONE DISEASE (ADULTS) STUDIED IN THE LAST FIVE YEARS IN WHICH THE MAIN COMPLAINT WAS OF GENERALIZED ACHES AND PAINS

Ætiology	Number of cases	Pathognomonic radiological signs present in	Presenting symptoms	Plasma biochemistry abnormal in
Steatorrhœa	10	8	Most of the following: Vague generalized "rheumatic" pains Waddling gait .. Muscular weakness Pain in low back and/or both thighs .. Tender ribs .. Stiffness of joints (rare)	All of these
Renal-glomerular failure ..	7	6		
Renal-tubular failure	7	5		
"Vitamin-D resistant" osteomalacia	9	7		
True adult vitamin-D deficiency	3	2		
Ureterosigmoidostomy ..	2	2		
Primary hyperparathyroidism with bone disease	4	4		
Osteogenesis imperfecta tarda	2	0	Low back pain Hip pain .. Severe back pain, loss of height, .. rib fractures .. Backache, more rarely rib pain ..	None of these
Idiopathic osteoporosis ..	7	7		
Senile osteoporosis	innumerable	all		

failure which have been already discussed by Drs. Rose and Lumb, we have also studied some metabolic bone diseases due to several other causes. The most common is probably that usually described under the name "vitamin-D resistant" osteomalacia. This condition is also associated with a renal-tubule leak for phosphate with few, if any, other signs of renal dysfunction. This group is certainly heterogeneous (Dent and Harris, 1956). Our 3 cases of vitamin-D deficiency require commenting upon. It is hardly possible to believe that this can occur in adults in this country since adult requirements are so small and the general level of nutrition adequate enough. For the same reasons, but with reference to the U.S.A., Albright and Reifenstein (1948) have stated "The authors are cognizant of no single case of osteomalacia in the United States due to simple vitamin-D lack. . . ." However, we have no doubts about the authenticity of our 3 cases and as all of them had reasonable worldly means but suffered only from curious ideas about food, further cases could presumably occur anywhere, even (perhaps especially) in the U.S.A. One of these cases will be mentioned in more detail below: the diet of another with brief clinical details has been described by our dietitian (Hill, 1956) and a brief reference to the third has been made by McCance (1953). As to the other diseases, the bone disease complications of ureterosigmoidostomy and of primary hyperparathyroidism are now well known. Although Table I is made out in the hope of giving some idea of frequency of incidence in the various kinds of bone disease, it is, of course, very inaccurate in this respect, as, apart from their small numbers, there is considerable selection in submitting patients to us.

It will be seen from Table I that the general symptomatology of the further bone diseases I am now introducing is similar to that described by Dr. Rose and Dr. Lumb for the special cases of steatorrhœa and renal dysfunction. Indeed, as far as the particular bone manifestations are concerned there may be no difference at all. However, associated additional findings in the history and clinical examination may be diagnostic. Note especially that in a small proportion of cases the skeletal X-rays appeared quite normal. Some

of these had very severe symptoms. The X-ray changes of the further cases shown in the bracket in Table I, when present, were usually indistinguishable from those in steatorrhœa and renal failure (Figs. 1 and 2A, B). An interesting additional point can, however, be made,



FIG. 1.—Pelvis of a patient suffering from one of the so-called "vitamin-D resistant" forms of osteomalacia. There are Looser zones in both ischiopubic rami and a further small one on the inner rim of the pelvis opposite the right femoral head. The patient was severely crippled by the pain but fortunately was diagnosed before symptoms had been present for long: there is therefore not much deformity. The clinical history of this patient was described by Rose (1956).



A B

FIG. 2.—Index finger of a patient suffering from osteomalacia associated with neurofibromatosis. In A, taken before treatment with vitamin D began, gross erosion of the terminal phalanx is visible and also subperiosteal erosions in the mid-phalanx, both of which we now interpret as being due to secondary hyperparathyroidism, a rare feature in this form of osteomalacia. In B we see the beginning of reformation of the phalanx after some months' treatment with vitamin D. This patient had also developed an osteoclastoma in her maxilla, which is a further sign of hyperparathyroidism.

namely that mixed osteomalacic and hyperparathyroid changes were comparatively uncommon in any of the ætiologies shown in Table I except in the case of renal-glomerular failure, when they were usually present together. The importance of the plasma biochemistry is well shown. It is mainly by this means that the cases have been diagnosed in the first place. I have also added to Table I three other kinds of bone disease which may also present in somewhat similar ways, although the symptoms are usually less generalized. Unfortunately our treatment for these is much less satisfactory.

Perhaps it would be simpler now to stress the clinical resemblance to steatorrhœa and renal disease, shown by one of these further causes of osteomalacia, by describing the relevant case history:

Mrs. L. R. A housewife, aged 46, referred to me by Dr. Cedric Shaw for investigation of "a great variety of skeletal and muscular pains coupled with increasing lassitude and embellished by a multiplicity of symptoms relevant to every single one of her visceral systems". Dr. Shaw added that she was clearly a very hysterical type of person and that no definite physical signs could be elicited apart from tenderness over the whole thoracic spine and a flinching whenever her abdomen was palpated. There was obvious dramatization and a long history of marital disharmony. X-rays, B.M.R., E.S.R. and full blood count were normal but, "as an afterthought", Dr. Shaw had determinations done of her plasma calcium, phosphorus and phosphatase levels. These showed abnormalities which suggested the possibility of metabolic bone disease being present.

On admission to the metabolic ward we fully confirmed the presence of plasma abnormalities. Her calcium was 8·8 mg./100 ml.; phosphorus 1·8 mg./100 ml.; alkaline phosphatase 20 units (K–A). Other electrolyte levels and blood tests gave normal results. Renal function was normal but urine calcium excretion averaged only about 20 mg./24 hours. Her bone X-rays and fat balance were normal.

Her history was interesting. It began with pain in her left hip twelve years previously: this was treated with heat and massage, but after a brief improvement pains returned and spread also to the right hip. She was otherwise fairly well till two to three years ago, when aches and pains began in other parts—arms, hands, thighs, ankles, chest, and the whole of the spine. Her bones became tender to touch and she suffered particularly from chest pain, especially when turning over in bed at night. To avoid being awakened by involuntary movements during sleep she had had to arrange her bed with bolsters on either side of her. She slept flat on her back in the groove thus formed. Nevertheless, on waking she felt as if she had been "beaten all over". It took her about an hour to get dressed. Her pains prevented her from going shopping or walking freely. She had noted muscular weakness, especially on going upstairs, when she needed to pull herself up by the banisters.

Our diagnosis on the basis of history, clinical and biochemical findings (and in spite of the normal X-rays) was of osteomalacia, but we were much puzzled as to its ætiology; but further study of her history revealed that although she ate well, and indeed looked very well nourished, she had always rigorously avoided fatty foods such as margarine, eggs, milk, oily fishes, &c., and had also avoided exposure to the sun in recent years. We estimated that her chosen diet had contained less than 20 units daily of vitamin D. Our suspicion that her bone disease was due to defective oral intake was subsequently fully confirmed by our studies of her metabolic and clinical changes before and after small oral doses of vitamin D. She is now almost symptom free, although still as peculiar as ever mentally.

Discussion

I hope that by now the point Drs. Rose, Lumb and I are trying to make has been made clear. It is that many cases of metabolic bone disease for which there is excellent treatment may in adults (the equivalent children's diseases usually present first with visible deformity) present with generalized aches and pains, usually rather vaguely localized and without any other obvious clinical features. These patients may be severely disabled, and although the diseases are all uncommon, they are gratifying to diagnose and treat. The problem therefore remaining is the very difficult one of picking out the one or two patients with metabolic bone disease (especially those without gross deformity or body disproportion) from the hundreds of others who also have aches and pains for other reasons. I can only suggest the following course of action as being practicable, as well as reasonably likely to succeed.

In the first place the clinical evolution common to all these cases should be very closely studied and remembered, bearing especially in mind the grave danger that the whole thing may appear to be entirely psychological. If the history is suggestive, and there will be many such cases, I think the urine should be tested routinely for the presence of protein (to pick out the renal cases) and for calcium with the Sulkowitch reagent (to pick out the low calcium excretions of many forms of osteomalacia). In both these cases the problem of urine concentration must be borne in mind for a very dilute urine cannot be properly tested and it is worth getting the patient to return with a morning specimen if necessary. (It is usually sufficient to look at it and only test specimens that appear reasonably yellow.) A case of severe renal damage will, of course, be unable to pass a strongly yellow urine, which in itself should arouse suspicion and be specially looked for. If there is still anything suspicious about the patient's history and preliminary urine tests, then further skeletal X-rays should be done, as well as blood tests, along the lines previously described (Dent, 1956), namely with respect to the plasma calcium, phosphorus, phospatase, bicarbonate and urea levels, and urine calcium output. If any of these are definitely abnormal, full and thorough investigation is justified and will not be too much of a burden since only a very small number of patients will survive this sorting and they will nearly all be genuine cases for whom we can do a great deal by medical treatment.

The treatment of these cases may sound surprisingly simple. It mainly comprises vitamin D with or without alkalis. There are serious dangers, however, of wrong dosage, the

required amounts varying considerably from case to case. Patients receiving treatment must therefore be carefully supervised. There is sufficient in the literature already about the treatment of steatorrhœa and of renal-tubular osteomalacia (Albright and Reifenstein, 1948). The renal-glomerular cases are more difficult and are not adequately covered as yet. We have considerable unpublished work on this subject which awaits longer follow-up of our cases. The treatment of so-called "vitamin-D resistant" ones has been reviewed recently by Dent and Harris (1956). There is still some doubt as to whether all the cases can, as we ourselves believe, be cured; and indeed Brailsford (1952) has described a case of typical osteomalacia that could not be cured with vitamin D, coining for it the new name of "osteogenesis exhausta". We have not yet come across such a case ourselves.

This review does not include all known causes of metabolic bone disease. Many interesting further examples such as that, for instance, following partial gastrectomy (Pyrah and Smith, 1956), or chronic liver disease (Atkinson *et al.*, 1956), or neurofibromatosis (Swan, 1954) have been briefly described already or are currently being further investigated. We have deliberately made no mention of other endocrine disorders such as Cushing's syndrome, acromegaly or eunuchoidism, all of which may present occasionally with pain due to bone disease. There is usually, however, in these cases much to take note of that would lead the patient to be first referred to an endocrinologist or general physician. Our attempt in this symposium was to describe cases very likely to be referred for treatment to Physical Medicine departments in view of the fact that the associated features which could lead to a correct diagnosis may require considerable looking for, and are never obvious at sight.

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SUMMARY

(1) Osteomalacia may be a cause of severe, vaguely localized, generalized aches and pains in a patient not otherwise presenting notable clinical signs. While osteomalacia of a particular ætiology may be rare, there are many different ætiologies which together provide us with a moderate number of cases.

(2) An attempt has been made to define more closely the clinical features of osteomalacia. The history may sometimes be characteristic and the X-ray signs often pathognomonic and accompanied by the signs considered specific for hyperparathyroidism.

(3) Whatever the ætiology, the clinical signs and skeletal X-rays may be indistinguishable.

(4) The existence of occult forms of renal failure and steatorrhœa presenting only as osteomalacia is stressed.

(5) In all these cases the bone disorder and associated symptoms can be cured independently of the progress of the renal or other disease.

(6) Rough methods are suggested for distinguishing these cases from the large number of other patients with aches and pains.

Section of Obstetrics and Gynæcology

President—R. A. BREWS, M.D., M.S., F.R.C.S., F.R.C.O.G.

[*March* 22, 1957]

The Ætiology of Fibroids

By PERCY MALPAS, F.R.C.S., F.R.C.O.G.

ALTHOUGH fibroids are the commonest of tumours, many aspects of their origin, their growth and their multiplication are still obscure. Largely this is due to the congruity between their structure and that of the tissues in which they grow. All the same, any explanation of their origin can only be based upon this congruity, or in other words their cause must be sought among the circumstances or conditions existing within the uterus itself; for whatever general factors may be concerned—such as age, childlessness, race, hormonal and growth factors—the immediate origin and structure of every fibroid is contingent on conditions obtaining in the local or intra-uterine causal field. This general principle was set out by Aristotle in the treatise "On the Parts of Animals". Discussing the nature of causation in biological phenomena Aristotle drew a sharp distinction between what he called hypothetical necessity and absolute necessity, defining absolute necessity as "such necessity as exists between substances and their inherent properties and characters". It is with the absolute cause of fibroids, that is their interpretation in terms of the structure and dynamics of the myometrium, that the present paper is concerned.

Exception may be taken to calling these tumours fibroids. The reason is that the term is a convenient and non-committal label which does not prejudge the issue. To call them myomas or fibromyomas is to beg the question, at all events in the present context, for the hypothesis to be proposed and considered is that these tumours are not true neoplasms, and that they arise and grow as the result of unresolved stresses in the myometrium.

The material falls into four sections: first the distribution patterns of fibroids, next the internal structure of established fibroids, next the evidence for the potentiality of stresses in the normal myometrium, lastly the structure of seedling fibroids.

THE DISTRIBUTION PATTERNS OF FIBROIDS

Provided that no one of a set of multiple fibroids is too large, their distribution in the uterus conforms to one of two general patterns. The reason for excluding any tumours much larger than a golf ball is that then the patterns become too complicated to analyse.

In the first and less important type of distribution, small fibroids, seldom more than 2 cm. in diameter, are scattered irregularly over the surface of the uterus. The distribution does not conform to any regular pattern. These tumours seldom grow to any size. This is shown by the frequency with which they are discovered accidentally when the uterus is removed for some other reason in women of 40 years or more.

The second type of distribution is the more important, not only for its theoretical bearing, but also because the tumours in this type undergo progressive growth and progressive multiplication. Almost invariably one fibroid in the set or pattern is larger than the rest. Its usual site is in the median sagittal plane of the uterus at the junction of the middle and inner thirds of the muscle wall, at a level roughly corresponding to the junction of fundus and body. This position corresponds to an interface between two zones of the myometrium. For convenience this largest tumour will be called "the dominant fibroid" in the following description.

The dominant fibroid is surrounded at varying distances by smaller tumours. These latter decrease in size as their distance from the dominant increases. Also the space between the secondary tumours themselves tends to increase with their distance from the dominant tumour (Fig. 1).

If it is assumed that the largest or dominant tumour is the oldest in the set, the progressive

decrease in size of the secondary tumours suggests that in some way or other their origin is contingent upon the presence of the dominant tumour. How could this arise? Possibly for this reason, that as a fibroid grows a considerable tension is set up both in the tumour itself and in the enveloping myometrium. This pressure is evidenced by the way the cut surface of a fibroid becomes convex, by the way that fibroids shell themselves out when bisected during the course of a myomectomy, by the force required to push a partially extruded fibroid back into its bed after it has been partially mobilized by an incision through its capsule immediately after a hysterectomy. This pressure sets up counter-pressures wherever any resistance is met with, and at the points where pressure and counter-pressure become equalized, energy is liberated and a condition of localized stress is set up. The situation is very similar to that obtaining in a crankshaft. Usually the secondary tumours are situated below the dominant tumour, along a line between it and the cervix, and the explanation of this pattern may be that the pressure exerted by the dominant tumour is more likely to meet a counter-pressure from below because of the relative fixity of the lower part of the uterus.

According to such a view fibroids are self-propagating tumours, that is to say that the presence of one fibroid induces the growth of others. There is some clinical evidence bearing on the problem. It is common to find a single symptomless fibroid in a young woman, and quite reasonably such a tumour may be left alone in the hope of pregnancy. Often it stays single and stationary in size for a year or so, and then fairly quickly fresh fibroids appear in an increasingly rapid succession, until at the inevitable operation the uterus is found stuffed with small secondary tumours, so many indeed that a hysterectomy usually proves necessary. The multiplication of the tumours follows a geometric curve, as indeed would be expected if the fibroids are self-inducing. That the small subperitoneal tumours remain small and isolated may be because of their position on a free surface where secondary stresses are not set up. Submucous and intraligamentary tumours likewise have a tendency to remain single.



FIG. 1.—Chains of fibroids in median vertical plane. Dominant tumour showing spiral structure, more marked in its outer half. Note diminishing size of secondary tumours and the increasing distance between them.



FIG. 2.—Two subperitoneal fibroids, 1 to 2 cm. across. Tumour on left shows linear mode of spread.

THE INTERNAL STRUCTURE OF FIBROIDS

Fibroids do not develop in a centrifugal manner from a central nucleus. Their usual spherical shape is solely due to their compression by the surrounding myometrium. Their true form is that of an irregular spiral with a varying number of secondary offshoots. This is shown by simple inspection of the cut surface of any soft fibroid with well-marked whorls but even more clearly by dissecting a fibroid under a dissecting microscope so as to separate the whorls, when the spiral shape becomes very evident. The spirals are usually more defined in the outer or peritoneal half of the tumour. Again the primitive shape is seen quite clearly in many of the small subperitoneal tumours which are less subject to compression (Fig. 2). In other words fibroids grow in a linear manner, a mode of growth most consistent with the view that their shape is determined by stresses in their structure. The almost constant occurrence of secondary nodules budding off the main tumour suggests that a dominant tumour induces secondary tumours not only at a distance but also locally. Certainly the

offshoots are not simple extensions of the primary tumour. Indeed their attachment to the dominant tumour may be quite tenuous.

Knots in wood are the resultants of stresses set up in growing tissues. The pattern exhibited by a knot in a piece of wood certainly bears a superficial resemblance to a fibroid, and if, indeed, a motto were wanted a saying of William Blake would be appropriate: "I can look at a knot in a piece of wood till I am frightened at it."

The Origin of Fibroids

When we consider the origin of the earliest seedling, it seems reasonable to assume that the seedling develops from causes similar to those which determine its continued growth. At all events such an assumption is certainly economical. To examine it entails, first, a consideration whether the potentiality of internal stresses exists within the myometrium as compared with plain muscle elsewhere in the body; and second, an examination of the microscopic structure of the seedling fibroid.

The Structure of the Myometrium

The myometrium is not homogeneous, but exhibits two sorts of differentiation. To begin with, its component muscle bundles are not straight but are disposed as a system of interlacing spirals. This is a consequence of the shape of the uterus. The uterus is an irregular solid, and in all irregular solids the lines of force along which the muscle bundles lie are not straight but geodetic—the shortest distance between any two points being a spiral curve. Because the bulk of the myometrium is composed of such interlacing spirals a low power magnification gives the fallacious appearance of an undifferentiated feltwork. Similar considerations indeed apply to the heart muscle, the heart too being best regarded as an irregular solid. The general problems of the structure of such tissues have been discussed by D'Arcy Thompson (1942) in "Growth and Form", and Shearer, in 1953, has drawn attention to the geodetics of the uterus.

Now in any system of interlacing spirals, there is a greater potentiality of internal stresses than obtains in tissues in which the muscle fibres are arranged in simple sheets at right angles one to the other, as is the case in the alimentary tract, with the exception of parts of the œsophagus, the stomach and the duodenum; by the way, these latter parts of the alimentary tract are almost the only sites in which the rare extragenital myomas appear.

Besides a spiral differentiation the myometrium is also divided into zones. While the zonal arrangement varies a good deal in definition it is common enough to be significant (Fig. 3).

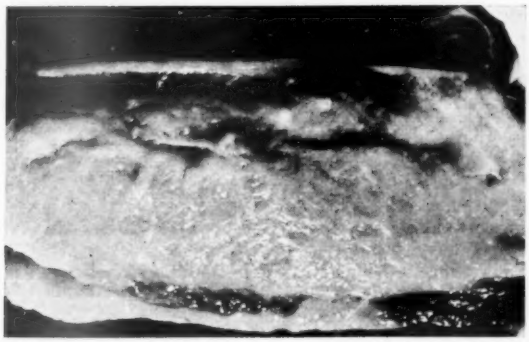


FIG. 3.—Enlarged photograph of whole thickness section of normal uterus (peritoneal surface uppermost). Note narrow outer zone and groove between middle and inner zones and "arcade" arrangement of bundles of inner zone, more noticeable on left.

It is more pronounced in the uteri of older women. The outermost zone, some 2 to 5 mm. thick, is dense. In it the muscle bundles are disposed symmetrically and mainly as a longitudinal sheet, the spiral disposition being less marked than obtains deeper from the surface. It is in this outer or cortical zone that the non-progressive subperitoneal fibroids occur.

The middle and inner zones constitute the bulk of the myometrium. They are separated by an interface in which run the main intra-uterine branches of the uterine artery and often this interface is marked in a cut surface by a narrow groove. The middle zone is the denser

of the two, in the inner zone the spiral disposition of the muscle bundles is more prominent (Fig. 4).

It is in the interface or partition between the middle and inner zones that a fibroid usually first appears, as indeed would be expected to be the case if an internal stress is its cause.

So far then there is some evidence from the heterogeneity of the uterus that the potentiality of internal stresses exists, but it may be asked what bearing this could have on the genesis of a seedling fibroid. An explanation could be that when a normal uterus contracts, as it does throughout pregnancy and to a lesser extent during every menstrual cycle, energy is liberated and under normal circumstances is expended in a change in shape of the organ. If for some reason or other, no change of shape is possible, by reason for instance of disuse changes in the myometrium, or increased viscosity in the matrix of the muscle spirals, or limitation of the uterine mobility by inflammatory appendage disease or endometriosis, the unresolved energy must be dissipated by the production of localized stresses, stresses which induce a local tissue reaction determining the appearance of a seedling fibroid. Before puberty and after the menopause, at those periods when the uterus is quiescent, fibroids never develop; after the menopause existing fibroids cease to grow. Furthermore fibroids seldom make their first appearance late in the reproductive period of life. In this regard the work of Fletcher Shaw and others on the histology of chronic metritis may well be relevant. For that matter in cases of pure hypertrophy of the uterus, which may weigh as much as 10 oz., fibroids are seldom encountered, perhaps because the internal structure of these uteri is normal. The viscosity and semi-fluid nature of the tissues are very apparent when an unstained fresh section of a fibroid and the surrounding myometrium is examined under a low power. Fixed and stained sections, necessary as they are, fail to show their plasticity.



FIG. 4.—Dominant fibroid, size of pea, in median vertical plane between middle and inner zones. Rough semicircle of seedlings to outer side. Outer zone of myometrium very well defined.

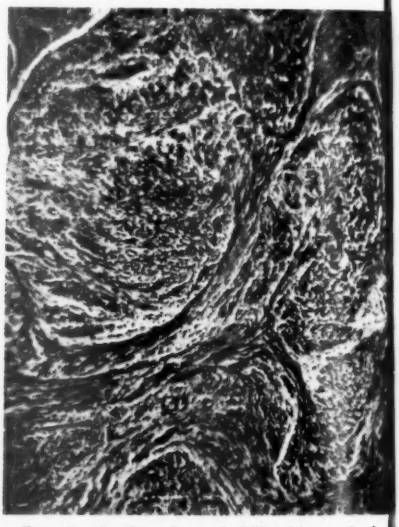


FIG. 5.—Section through "fibroid area", showing spiral bundles of myometrium enclosing and merging with seedling. Low power.

THE MICROSCOPIC APPEARANCES OF SEEDLING FIBROIDS

Two features of the structure of seedling fibroids have a bearing on the present issue. The one is their spiral structure, a point already discussed (Fig. 5). The other is their lack of any capsule, the encapsulation of larger fibroids being a secondary phenomenon. Willis (1953) states that "the usual view that myomas are encapsulated needs revision, for while it may be true of large tumours, it certainly does not apply to many small ones. Minute myomas, even when apparently well circumscribed to the naked eye, are often not sharply separable from the surrounding muscle microscopically". So true is this observation that it is often difficult to say where the normal myometrium ends and a fibroid begins, certainly by a microscopical examination. At the base of the seedling there is a gradual transition from one to the other, the muscle bundles showing an increasing distortion as they near the tumours and the cells

themselves progressively changing from the normal to the more primitive forms in the growing points of the seedling (Fig. 6).



FIG. 6.—Small intramural fibroid with extension into myometrium at 2 o'clock. Encapsulation of extension incomplete.

SUMMARY

There is some evidence to support the view that the origin, growth and propagation of fibroids can be interpreted as the result of unresolved myometrial stresses. The hypothesis certainly saves some, if not all, of the appearances without reference to any of the general factors usually invoked. This is not to say that such general factors are without significance. For instance, part of the answer to the genesis of fibroids is to be sought in the reasons why fibroids are at least three times as common in coloured women. Nevertheless, whatever the role of the general causes, the intimate structure and distribution patterns of fibroids can only be explained in terms of occurrences within the uterus itself.

Finally one general conclusion seems important, that fibroids are not neoplasms in the ordinarily accepted sense of the term, but local reactions arising in a tissue with a unique dynamic structure and one which is often subjected to long phases of physiological disuse.

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Habitual Abortion

By V. B. GREEN-ARMYTAGE, M.D., F.R.C.P., F.R.C.S., F.R.C.O.G.

The Institute of Obstetrics and Gynæcology, Hammersmith Hospital

IN 1938, Malpas postulated that the chances of a woman having a full-term baby after 3 abortions was 27% only. In 1953, Swyer and Daley contested this and stated that the chances were 50%. Professor McClure Browne and the present writer think that there exists a hard core of cases of abortion which are due to congenital weakness or acquired trauma of the fibromuscular ring at the junction of the lower uterine segment and the anatomical internal os. The trauma may be due to the passage of a large baby, large dilators, or the faulty application of forceps, and results in herniation of the conceptus with quick, painless and complete expulsion of the fœtus—a condition that will recur again and again according to the degree of damage present.

In 1950, Lash and Lash devised an operation when the defect was in the anterior segment of the cervix—which must be very rare. In 1954 Shirodkar described his operation using fascial strips or nylon tape to encircle and constrict the cervical canal at the level of the internal os (Shirodkar, 1955). At the Institute we have simplified this technique by using one or two filaments of nylon, size 7.

In the non-pregnant patient, the condition of insufficiency at the internal os is considered to exist if (1) The patient has had 2 or 3 abortions, quick, painless and complete, with or

without a history of trauma. (2) A No. 4 Hegar dilator can be passed with ease and without pain through the cervical canal into the uterine cavity. (3) A cervicogram demonstrates the dilated canal—using a small finger stall firmly attached above the rubber cone of a Lipiodol syringe.

In the pregnant patient, often being seen for the first time, the criteria are: (*a*) The previous history. (*b*) A patulous external os which admits the finger almost to the internal os, soft and flabby.

The author has done seven of these modified Shirodkar operations: Three have gone to full term and been confined—two by Cæsarean section and one naturally. One[1] is in her 38th week and is particularly interesting as she was first seen in her 17th week after rupture of the membranes. One is in her 15th week and is worth recording as she had her second Shirodkar operation at the 12th week of pregnancy. One is in her 12th week. One has not conceived.

The operation must not be undertaken lightly, but if the indications exist, there are three essentials in the technique. (These were demonstrated by means of a coloured film.) (1) The needle must take a bite of the anterior surface of the cervix. (2) The nylon must be knotted in the incision on the posterior surface of the cervix. (3) The Macewen hernia needle or Reverdin needle must be blunt.

Unless otherwise indicated, Cæsarean section is not necessary.

If the ligature is seen before or during labour, all that is needed is to grasp the knot ends as they protrude from the posterior incision and cut the nylon filament. In such a case, if and when more children are desired, the operation must be repeated.

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[1]The nylon suture was removed by the author; the confinement was normal.

Mr. David Currie showed a film illustrating the **Technique of Wertheim's Hysterectomy.** His results in 214 cases treated during the last twenty years were as follows:

	Per cent
Five-year survival rate	79·3
Five-year survival rate, stages 1 and 2*a* ..	87·3
Ten-year survival rate	77·2
Ten-year survival rate, stages 1 and 2*a* ..	86·6
Glands	
30% of all cases had malignant nodes	
Five-year survival rate	55·5
Five-year survival rate, stages 1 and 2*a* ..	73·6

[*April* 26, 1957]

THE following specimens were shown:

Primary Torsion of the Fallopian Tube.—Mr. G. L. BOURNE.

Melanoma of the Vulva.—Dr. G. W. KORN.

Stein-Leventhal Syndrome.—Dr. B. H. DAWSON.

Acute Axial Torsion of a Fibromyomatous Uterus.—Dr. NIGEL GOURLAY.

Hydrosalpinx following Sterilization by Crushing and Ligating the Fallopian Tubes.—Dr. R. W. GRAYBURN.

Rupture of the Lower Uterine Segment Following a Modified Brandt-Andrews Manœuvre on a Patient with a Partial Placenta Accreta.—Dr. J. C. HARTGILL.

Peripheral Gangrene During Pregnancy.—Mr. HAROLD FRANCIS.

Forelying Constriction Ring Associated with Postmaturity and Intrauterine Fœtal Death.—Mr. W. K. SUTTON.

Section of Orthopædics

President—E. STANLEY EVANS, C.B.E., F.R.C.S.

[*February* 5, 1957]

The Problem of the Trans-cervical Fracture [*Abridged*]

By DENYS WAINWRIGHT, F.R.C.S.Ed.

THE trans-cervical fracture of the femur continues to present a challenge to orthopædic surgeons, and increasing longevity makes it even more important that we should be able to offer the patient of 55 or 60, who sustains this injury, at least ten years of comfortable activity.

A recent study of the blood supply of the femoral head (Hulth, 1956), using a new angiographic technique in which opaque fluid is injected directly into the osseous tissue of the head, has shown that synovial bridges containing blood vessels remain intact even when gross displacement of the fracture occurs. This is particularly true of the inferior retinacular vessels which are not so closely related to the under-surface of the neck of the femur. Although it is probable that a good deal of the vascular change occurs at the time of the accident, preservation of these precarious life-lines of the femoral head must depend to some extent on careful handling of the patient after the accident. Early immobilization and correction of the deformity will prevent kinking of the vessels, and gradual reduction of the fracture by traction is less likely to damage the blood supply of the head than the often vigorous traction and rotation manœuvres which are sometimes necessary to secure an accurate reduction. Such a reduction is essential if internal fixation is to be successful.

The difficulties which are experienced from time to time in fully reducing these fractures by manipulation have in our experience been overcome by gradually reducing the fracture using a modified form of Russell traction—the traction being applied by means of a Steinmann pin through the upper end of the tibia. An upward pull from the outer side of the pin will gradually correct the external rotation deformity. Internal fixation of the fracture is postponed until full reduction has been obtained with the additional advantage that the operation can be performed at a convenient time. It is in many cases possible, by increasing the traction, to slightly over-correct the deformity, allowing the femoral head to tilt over into a coxa valga position, until the fracture resembles an abduction type. If in this position the fracture is then immobilized with a Smith-Petersen pin, or a type of blade plate, inserted well below the great trochanter in a fairly vertical direction as far as the sub-chondral region of the head, we have established the optimum mechanical position for union to take place. Immobilization of the fracture in any degree of coxa vara imposes an almost insuperable strain at the fracture site, with inevitable delay in union.

Sub-capital fractures and fractures with more or less vertical fracture line in which the blood supply is very likely to be severely damaged must be kept especially stable. Immobilization must be such that stability is maintained even after creeping substitution of any necrotic bone has begun. In the belief that in such cases complete immobilization can best be achieved by transfixing the head, we have, in a small number of cases, driven the nail through the head about ¼ in. into the acetabulum (King, 1939). Provided the weight-bearing portion of the acetabulum is avoided and the pin is not driven through the upper part of the femoral head, where it is likely to devitalize the outer third of the head, penetration of the head causes surprisingly little disability and the pin can be left in position for many months until radiological evidence of bony union is present.

In short, it is suggested that in the younger age group where the operation is not being performed as a life-saving measure or merely to ease nursing difficulties the transcervical fracture should be handled carefully, should be reduced gradually until it is slightly over-corrected, and if possible immobilized with a Smith-Petersen pin inserted in a fairly vertical direction; and that there is a place for complete transfixion of the head in the high fracture with a small fracture angle.

Causes of failure.—Provided the fracture unites, many of these patients will be able to contend with a localized area of necrosis of the head. It is pseudarthrosis which is responsible for most disability following this fracture.

The recognition of the early signs of failure and the beginning of non-union implies a careful follow-up, with X-rays repeated at intervals of a few weeks.

a) Primary instability.—These are cases in which the pin breaks loose within the first few weeks and these failures are usually due to technical errors and are much less frequent in experienced hands. When, as sometimes happens, the failure is due to inability to reduce the fracture, then I believe the treatment likely to give the highest percentage of reasonably good results is a displacement osteotomy of the McMurray type.

(*b*) *Secondary instability.*—Here the pin slowly ploughs its way through a more or less avascular head many months after the original operation. Osteotomy in these cases will provide reasonable stability but if the head is avascular union of the fracture cannot be expected. In such cases complete replacement of the dead head by a prosthesis will probably give a higher percentage of good results. If a reasonable amount of femoral neck is present, if the prosthesis is inserted in an almost vertical direction, if the patient is fairly light and is not expected to lead a very active life, a prosthesis of the Judet type can be expected to succeed. If, on the other hand, we are faced with complete non-union and little of the femoral neck is preserved, then a larger type of metallic prosthesis is indicated.

(*c*) *Late osteo-arthritic changes.*—Many of these patients do develop localized areas of necrosis of the hip with marked osteo-arthritic changes. These do not necessarily progress, nor cause much disability. In other cases, particularly those associated with an increasing coxa vara, the symptoms become progressively worse. In this particular age group the choice must lie between some type of arthroplasty and osteotomy. In my opinion a displacement osteotomy using internal fixation is likely to give the better long-term results.

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Mr. R. C. F. Catterall showed a film on "Chemopallidectomy" by kind permission of its originator, **Dr. Irving S. Cooper** of New York. The procedure was used in the treatment of Parkinsonism, athetosis and other conditions where it was believed that the essential lesion lay in the globus pallidus region. After some success with the very difficult operation of ligation of the anterior choroidal artery, Dr. Cooper's present method was to pass a brain cannula into the globus pallidus and, after a preliminary test injection of local anæsthetic, to inject alcohol.

The results illustrated were dramatic in the extreme and appeared to be permanent. Tremor disappeared completely in the contralateral limbs and the power of co-ordination returned. Good results were obtained by Dr. Cooper in about 70% of cases. Mr. Catterall and subsequent speakers stressed that other neuro-surgeons had not yet produced comparable results, the difficulty apparently lying in the exact localization of the globus pallidus.

The Relief of Pain in Paget's Disease (Osteitis Deformans)
[Abridged]

By ROY H. MAUDSLEY, F.R.C.S.

PAIN has been a common feature of osteitis deformans since first described by Sir James Paget in 1877. He wrote ". . . in earlier periods, and sometimes through all its course, the disease is attended with pains in the affected bones, pains widely various in severity and variously described as rheumatic, gouty or neuralgic, not especially nocturnal or periodical . . .". In eighty years little has been added to this description.

Many patients with Paget's disease also have osteoarthritis in the lumbar spine and hips, and some of their pain is attributable to this. It is the constant boring pain which bears so little relationship to other forms of limb pain that I wish to consider. The disappointment with treatment is reflected in the numerous methods tried and largely abandoned. The success attending the relief of unusual pain in the limb in causalgia and Sudeck's atrophy, by blocking of the autonomic nervous pathways, suggested a trial of this for Paget's disease. The technique adopted was that of epidural anæsthesia.

Epidural anæsthesia.—The susceptibility of nerve fibres to anæsthetic solutions varies according to their calibre and medullation. Thus a fairly selective anæsthesia can be obtained if a weak solution is used. This is capable of affecting autonomic and some afferent pain fibres, which are of small calibre and either non-medullated or only thinly medullated, but will not affect the thicker afferent and efferent somatic fibres.

Though it is not known how or where the pain in Paget's disease originates, nor which fibres are responsible for its transmission, epidural anæsthesia affords a ready access to the smaller somatic afferent fibres known to convey some pain impulses, and to the autonomic fibres, also a possible pain pathway.

The spread of anæsthetic fluid within the epidural space is believed to be wide, as shown by radiographs after the epidural injection of Myodil. This may well be an asset in making exact localization less important. The epidural space lies between the walls of the spinal canal and the dura mater, and is continuous laterally with the intervertebral foramina. This space is traversed by the spinal nerves, covered by a sheath of dura mater.

Technique.—The patient lies in the lateral position with the painful limb uppermost. The interspace between the 1st and 2nd lumbar spinous processes is used. Under local anæsthesia

the spinal needle is passed into the interspinous ligament. The stilette is withdrawn and replaced by a 20 ml. syringe with 0·5% Xylocaine. As the needle is moved on with the thumb gently pressing on the plunger, a decreased resistance is felt as the needle enters the epidural space. The syringe is removed and the end of the needle is observed, to exclude a spinal tap, after which 10–20 ml. of the Xylocaine is injected.

Clinical trial and results.—10 patients suffering from pain in Paget's disease have been treated by epidural blocks over the last five years. Each had had pain in the pelvis or lower limbs for a period from several weeks to several years. The blocks were repeated when necessary, to enable the patient to remain in comfort.

In most cases there was immediate relief of pain, though not always complete, lasting from a few days to a few weeks, after which the pain recurred, but in some instances at a reduced level. Further injections again relieved the pain for varying intervals. Failures to relieve were thought to have been due to selection of a patient with predominantly osteoarthritic symptoms and possibly to injections outside the spinal canal. Two patients had spinal taps and had temporary spinal anæsthesia, though still with relief of pain.

Discussion.—The mode of action is uncertain. If one believes in a sympathetic reflex with afferent and efferent neurones, then it may act on the afferent fibres carrying pain impulses; or it might act on the efferent fibres modifying the vascular state of the limb.

In none of my cases was a sympathectomy offered since the pain was controlled by these blocks.

It is difficult to explain the long pain-free intervals following injection with local anæsthetic, but a similar variation exists after sympathetic blocks for causalgia, Sudeck's atrophy, &c.

Summary.—A preliminary report is made on a simple and effective procedure in the relief of pain in Paget's disease. The technique and the clinical trial and results are discussed.

Hydrocortisone in Tennis Elbow—A Controlled Series [*Abridged*]

By R. A. J. Baily, M.B., F.R.C.S., and B. H. Brock, M.B., F.R.C.S.

Any consideration of the treatment of tennis elbow must raise the question of its pathology and ætiology. A study of the literature reveals considerable variation of opinion, and Cyriax (1936) lists no less than twenty-six different pathologies described by various authors.

To summarize his conclusions and those of subsequent authors, the following alternatives appear to be best supported by factual evidence:

Extra-articular.—(*a*) A tear of the extensor origin with or without periostitis. (*b*) A degenerative lesion of the extensor origin. (*c*) Inflammation of the underlying bursa of Osgood.

Intra-articular.—Nipping of a synovial fringe in the radio-humeral joint.

The literature has been reviewed, and on balance the evidence is in favour of an extra-articular degenerative lesion associated with strain of the extensor muscles, but a synovial lesion may exist in some cases.

Treatment.—In 1953, Hollander described the use of hydrocortisone (compound F) in intra- and extra-articular joint lesions, and found it beneficial in tennis elbow. In this country Cyriax and Troisier (1953), Murley (1954), Quinn and Binks (1954), and Crisp and Kendall (1955) have reported favourably on its use. In a controlled series, Freeland and Gribble (1954) found little difference in the effect of hydrocortisone from 5% procaine, but the small numbers make the result somewhat inconclusive.

The purpose of the present series is to assess the specific effect of hydrocortisone as distinct from the mechanical effect of fluid injection into the affected area.

Material.—In all, 40 patients were treated, of whom 16 were male and 24 female, the average age being 45·5 years. In 10 patients (25%), there was a history of trauma, usually a direct blow on the epicondyle.

In 10 cases associated complaints of pain, with or without stiffness, of the neck and shoulder were noticed at some time, but in all cases the relief of symptoms by procaine injection into the tender area was made a criterion of diagnosis, and such associated symptoms were regarded as incidental.

Method.—The series was divided into two random groups, A and B, by selection of alternate patients. Group B was treated by the injection of 1–3 ml. of 2% procaine into the tender area, followed by manipulation by Mills' manœuvre. Group A received exactly similar treatment but the additional injection of 25 mg. (1 ml.) of hydrocortisone acetate.

The injections were all carried out by one of us (B. H. B.), while the other (R. A. J. B.), who was unaware which treatment had been given, examined the patients at one week, three weeks and two months after treatment.

Where symptoms were unchanged after three weeks a course of physiotherapy was instituted (Renotin ionization, heat and deep massage), and in 8 cases still unrelieved after two months a second injection of hydrocortisone was given.

The results were assessed at the end of two months, and the results of those patients who received a second injection are given separately below. 9 patients were followed up for less than one month owing to non-attendance.

Results.—The results have been graded as *cured*—relieved of all symptoms, *improved*—with slight symptoms on heavy use and/or persistence of tenderness, *unchanged* and *worse* (Table I).

TABLE I

Treatment	Cured	Improved	Unchanged	Worse
Group A				
Hydrocortisone and 2% procaine	10 (50%)	4 (20%)	5 (25%)	1 (5%)
Group B				
2% procaine	5 (25%)	5 (25%)	10 (50%)	—
Totals	15 (37·5%)	9 (22·5%)	15 (37·5%)	1 (2·5%)

Of the hydrocortisone group, 14 (70%) were cured or improved as compared with 10 (50%) of the control group. 5 (25%) of the hydrocortisone group were unchanged and 10 (50%) of the controls. The 1 patient who was worse was a very unstable personality seeking compensation for a supposed industrial injury.

An exacerbation of symptoms for twenty-four to forty-eight hours occurred in 10 (25%) patients. Of these, 5 were in Group A and 5 in Group B, their eventual results being 7 cured, 2 unchanged and 1 worse.

In 8 patients whose symptoms were unchanged at the end of two months, a second injection of hydrocortisone was given. Of these, 2 were in Group A and 6 in Group B. The results of this further injection were 3 cured, 3 improved, and 2 unchanged.

In 2 patients of the hydrocortisone group and 5 of the controls early relief of symptoms was followed by relapse, confirming the findings of others that the effect of hydrocortisone, as of other treatments, may be only temporary.

Of the 9 patients who attended for less than a month, 4 were cured, 2 improved, and 3 unchanged when last seen.

In addition to the above findings, the results were analysed in relation to age, history of trauma, length of history, the presence of associated symptoms in the neck and shoulder, and the presence or absence of previous treatment. None of these factors showed any significant effect on the pattern of the results.

Discussion.—Tennis elbow is a self-limiting condition whose natural course is rarely longer than eighteen months. Any assessment of treatment must therefore take into consideration the time factor.

The results of this series, although the numbers are small, confirm that hydrocortisone is effective in the treatment of tennis elbow, and that its action may be distinguished from the mechanical distension of tissues by fluid injection. Although relapse may occur, the use of hydrocortisone allows a higher proportion of successful results than other conservative measures within a limited period of time. The relief of symptoms has in many cases been dramatic. In those cases where recurrence has followed initial relief, or where one injection has proved ineffective, a second injection is frequently successful.

We are indebted to Mr. K. H. Pridie, Mr. A. L. Eyre-Brook, Mr. H. K. Lucas and Mr. M. P. McCormack for permission to investigate patients under their care.

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Section of Dermatology

President—Louis Forman, M.D., F.R.C.P.

[*January* 17, 1957]

Presentation of Diploma of Honorary Membership of the Section to Sir Archibald Gray

The President: I have a gratifying duty to perform which I know will give us all much pleasure. At the last meeting we elected Sir Archibald Gray as an Honorary Member of this Section, the highest honour which we can bestow upon any of our own Members or other dermatologists. Sir Archibald Gray has been a Member of the Section for forty-six years; he has held all the offices in the Section and he is our Senior Past President. Most of us have grown up under his guidance and this is therefore a very pleasant domestic ceremony.

Sir Archibald has been recognized and honoured in fields wider than our specialty but his active interest in dermatology and in our Section has been maintained. I have very much pleasure in presenting him with the Diploma of Honorary Membership with the hope that we shall enjoy his companionship here for many years to come.

Sir Archibald Gray: It is very kind of you to honour me in this way. My colleagues on so many occasions have done me so much honour that I scarcely know how to reply. I feel I cannot say more than to thank you very sincerely for your kindness.

CASES

Sarcoidosis with Skin Lesions Simulating Necrobiosis Lipoidica.—P. F. Borrie, M.R.C.P.

History.—A housewife, now aged 49, developed a fever in 1949 and was in hospital for three months. Examination at that time revealed right iridocyclitis, generalized superficial lymphadenitis but no other abnormal physical signs. During her stay in hospital she developed a transient left facial palsy and left hemiparesis and a localized thrombophlebitis in a vein on the left wrist.

Investigations.—Hæmoglobin 48%. W.B.C. count, normal total and differential. E.S.R. 10 mm. in the hour (Westergren). Plasma protein normal total and differential. X-rays of chest and extremities normal. Urine normal. Liver biopsy normal.

She made a steady recovery and her general health has since remained good. The iridocyclitis, however, persisted and progressed to uveitis and phthisis bulbi. The eye was removed in April 1956, histological examination showing sarcoidosis.

In July 1955 a non-irritant eruption appeared on both shins. Shortly after this superficial ulceration occurred in two small areas on the right shin taking seven months to heal. A month ago the eruption began to spread and fresh ulceration appeared.

The past and family histories are not relevant.

On examination.—On the front of both shins and the sides of the calves there is a patchy telangiectatic erythema. On the right shin there are two areas of depigmentation and atrophy, as well as a few superficial ulcers 0·5 cm. in diameter. There are also multiple, circular, discrete patches on the sides of the calves, with erythematous margins and slightly sunken waxy centres traversed by telangiectatic blood vessels. The spleen is palpable two finger-breadths below the costal margin, but no other abnormality was found.

Investigations.—Hæmoglobin 95%. W.B.C. 3,600, normal differential. E.S.R. 10 mm. in the hour. Plasma proteins normal. Chest X-ray normal.

Histology.—The epidermis shows atrophy. The corium exhibits several sarcoidal nodules. The collagen shows necrobiotic changes. Some smaller vessels show narrowing of their lumina.

Comment.—Since Goldsmith (1935) described the first case of necrobiosis lipoidica unassociated with diabetes mellitus, this type has been reported with increasing frequency. It is clear now that, in this country at least, the condition is commoner in non-diabetics than in diabetics. No definite ætiology, however, has been ascribed to it.

The cutaneous features of the present case are clinically typical of necrobiosis lipoidica and histological examination shows both collagen necrobiosis and sarcoid infiltration. There is both clinical and histological evidence of ocular sarcoidosis and this lesion commenced at the acute onset of the illness five years ago. An over-all diagnosis of sarcoidosis therefore seems reasonable.

My second case showing a similar symptomatology unfortunately did not attend, but a similar case was shown by Drs. O. L. S. Scott and G. A. Beck at a recent meeting of the St. John's Hospital Dermatological Society. In recent years an increasing number of cases of erythema nodosum have been shown to be the result of sarcoidosis and I think that the same thing will happen with non-diabetic necrobiosis lipoidica.

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Dr. Henry Haber: This case shows typical sarcoid histology. The collagen exhibits some scleroderma-like changes leading to the clinical appearance of necrobiosis.

Dr. G. A. Beck: The case which I showed at St. John's hospital on June 7, 1956, had lesions apparently typical of necrobiosis; it was only after the histological report suggesting sarcoid was received that we found that she had extensive typical X-ray changes of sarcoid in the lungs. We treated her with cortisone for quite a long time, at least the physicians did, with the idea of reversing the lung signs. There was no change in the lesions on the leg which were more typical even than these. I thought they were clinically indistinguishable from necrobiosis.

Dr. G. A. Hodgson: We do see these cases which look like sarcoid and I wondered if in such persons there might exist some sarcoid state of the skin so that the necrobiosis with vascular changes would then provoke more a sarcoid-like change instead of the ordinary appearance of necrobiosis.

Dr. D. S. Wilkinson: Out of my last 6 or 7 patients who appeared clinically to have necrobiosis, 3 have turned out to have sarcoidosis; 2 had typical involvement of other organs. All 3 had positive Kveim reactions, which were negative in the other cases. I am sure this is no chance association; it is too frequent.

Impetigo Herpetiformis.—M. FEIWEL, M.R.C.P., and D. FERRIMAN, D.M., M.R.C.P.

In September 1951, L. S., a housewife aged 46, was admitted to the North Middlesex Hospital as an emergency in prostration with a confusional state and a diffuse rash. The latter had commenced simultaneously on the inner aspects of the thighs and the front of the chest and had extended rapidly to cover almost the entire body-surface. Her obstetrical history included six normal deliveries and one miscarriage. No rash had ever been observed during gestation or in the puerperium. In her fifth pregnancy (1944) she developed a thyroid swelling, which in 1951 was accompanied by stridor and in June of that year a subtotal thyroidectomy was performed for colloid goitre. Post-operatively, spasmophilia with hypocalcæmia (serum calcium levels of 7·0 mg., and later 6·1 mg./100 ml.) occurred. She was treated with calcium orally as an out-patient and at one of these visits diplopia was recorded.

On admission.—Clusters of pinhead-sized pustules had already coalesced and the confluent areas were partly encrusted. The skin was œdematous and cracks were seen in the creases (Fig. 1). Within a few days delirium and hyperpyrexia (temperature 106° F.) ensued and continuous twitching and jerking movements were observed. These spontaneous movements were probably due to a combination of spasmophilia and profound constitutional disturbance. Chvostek's sign was not demonstrable, but the serum calcium was 5·0 mg. per 100 ml. Her leucocyte-count was 25,000 (92% polys.). She seemed moribund.

Treatment.—Corticotrophin (20 units, six-hourly) and dihydrotachysterol (5 ml. daily) with calcium gluconate (10 grains, i.m., t.d.s.) were promptly prescribed and within forty-eight hours there was a remarkable improvement; indeed she was now alert and the abnormal movements had entirely disappeared. Her temperature was returning to normal. The rash was subsiding and soon resembled exfoliative dermatitis with, however, the characteristic



FIG. 1.—Impetigo herpetiformis, clusters of pustules coalescing to form confluent areas; skin œdematous and cracking.

reddish-brown colour of impetigo herpetiformis. The hair and nails were shed and within a few months healing was complete.

Maintenance therapy consisted of thyroid with both calcium and vitamin D, orally, for her hypothyroid and hypoparathyroid states respectively. Now, five years later, she is in good health and continues to take thyroid (3 grains daily), vitamin D (25,000 units daily) and calcium lactate (10 grains t.d.s.). Impetigo herpetiformis has not recurred.

A brief account of this patient has appeared previously (Ferriman, 1953).

Discussion.—In 1872, Hebra described impetigo herpetiformis as a pustular eruption with serious constitutional symptoms affecting women in pregnancy or in the puerperium. It was later shown that this disease was neither confined to gestation and the puerperium nor to females. Moreover, constitutional disturbance may be absent. Although co-existent hypocalcæmic states are recognized, much of the earlier evidence on this point was purely clinical.

The clinical postulates of Hebra and Kaposi, as modified with time, were listed by Hall (1944), who stated that all attempts to prove an infectious or toxic basis had failed. Beek (1951) reviewed the literature and indicated the incidence of various clinical associations. Of 53 cases, 19 were idiopathic whereas 22 occurred during pregnancy and were accompanied on 12 occasions by hypocalcæmic states either proven or presumed. Another 12 patients had proven or presumed hypocalcæmia and most of these patients had undergone partial thyroidectomy. In view of the increased pituitary activity in pregnancy, it is of interest that one of the idiopathic cases had a pituitary tumour (Trýb, 1921).

The association, as in our patient, with a previous partial thyroidectomy is well documented, the literature revealing good evidence of hypoparathyroidism in 9 cases (Schardorn, 2 cases, 1921; Kyrle, 1926; Brill, 1928, whose case was later reported by Danisch, 1929; Lutz, 1928; Bohnstedt, 1933; Gans, 1933, whose case was re-narrated by both Wendt in 1934 and Schubert in 1936; Bartmann, 1937; Englefeldt and Gentele, 1950). These 9 cases were all women, whose ages ranged from 18 to 50. 2 were pregnant when their dermal lesions appeared. The interval between thyroidectomy and the appearance of the skin lesions varied from three months to twenty-nine years in the 9 patients, 6 of whom died. It is emphasized that 2 of the 3 patients who recovered differed from the rest of the 9 patients in that they alone received adequate treatment by modern standards for their hypocalcæmia. One patient (Gans, Wendt and Schubert) is of unusual interest since it was shown that cessation of this treatment led to relapse of the dermal lesions, which regressed after resuming treatment. A further point of interest concerns one of the patients in the group with pregnancy and hypocalcæmia. It is surmised that this patient had idiopathic hypoparathyroidism since, at her autopsy (Walter, 1922), there was no demonstrable parathyroid tissue.

The clinical picture of our patient exemplifies the severe form of impetigo herpetiformis and although a recent case report by Steppert (1954) includes photographs comparable with ours, his case was less fulminating.

Finally, our clinical impression that corticotrophin was decidedly beneficial must await further communications.

We wish to thank Dr. R. J. Calvert for help in the preparation of these comments.

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Dr. G. A. G. Peterkin: I have had two cases, one of a woman who had typical myxœdema and who responded to thyroid extract; there was apparently no damage to the parathyroids; the physician said she was a typical myxœdema and she has kept well since taking thyroid.

Dr. Feiwel: The ætiology of impetigo herpetiformis is unknown and no infective agent has definitely been incriminated.

The following cases were also shown:

Lichen Myxœdematosus.—Dr. J. E. M. WIGLEY, Professor W. ST. C. SYMMERS and Dr. D. L. REES.

(1) **Multiple Granulomata (Granuloma Annulare).** (2) **Acrodermatitis Continua with Vascular Changes in the Digital Arteries and Venous Channels.**—Dr. G. B. MITCHELL-HEGGS.

Acrogeria (Gottron).—Dr. G. B. DOWLING (*see Proc. R. Soc. Med.* (1957) **50,** 330).

(1) **? Tuberculoid Hansen's Disease.** (2) **Widespread Pigmentation for Diagnosis.**—Dr. J. D. EVERALL (for Dr. G. B. MITCHELL-HEGGS).

Calcinosis Circumscripta (Thiberge Weissenbach Syndrome).—Dr. N. A. THORNE.

Chronic Lymphœdema of Eyelids with Plastic Repair.—Mr. C. R. MCCASH and Dr. M. FEIWEL.

Congenital Malformation of Upper Limb—Hæmangiectasia Hypertrophicans, Klippel-Trenaunay-Parkes Weber.—Dr. M. FEIWEL.

? Multiple Fibromata; ? Hamartomata of the Fingers.—Dr. ROBERT BOWERS.

Hansen's Disease (Maculo-anæsthetic).—Dr. LOUIS FORMAN.

Dr. R. M. B. MACKENNA read a short paper entitled **Samuel Plumbe, the Forgotten English Dermatologist.**

Section of Surgery

President—ERIC A. CROOK, M.A., M.Ch., F.R.C.S.

[*February* 6, 1957]

The Surgical Significance of the Internal Architecture of the Liver [*Abstract*]

By MICHAEL HOBSLEY, M.A., M.B., B.Chir.

To the surgeon, the liver is an organ that bleeds excessively when cut. To the student of gross anatomy, the liver is preponderantly hepatic veins. These arise from the inferior vena cava near the superior margin of the liver as three main stems, the right, the middle and the left hepatic veins. (Usually the middle springs from, or takes common origin with, the left hepatic vein.) The hepatic veins fan *downwards*, defining three corresponding segments of liver, and the extent of anastomosis between these segments is uncertain though most investigators agree that there is some (Elias and Petty, 1952; Gans, 1955*a*). The left vein drains the classical left lobe, that is the area to the left of the falciform ligament.

The portal veins occupy less than half the volume of the hepatic veins. At the porta hepatis the main trunk of the portal vein divides into a short right and a long left division. Smaller branches fan laterally from these stems, and so tend to run at right angles to neighbouring hepatic veins.

The much smaller bile ducts and hepatic arteries run through the liver substance in close proximity to a portal vein branch, the three structures constituting the "Glissonian system". There are few vascular and no significant biliary anastomoses between contiguous branches, and the areas which these branches define may conveniently be studied by injection of any one of the three components of the system.

Thus post-mortem radiological visualization of the bile ducts shows most commonly the following pattern: *the common bile duct* divides into *right* and *left hepatic ducts;* the former drains the right half of the liver by two main ducts, an *antero-medial* and a *postero-lateral;* while the latter supplies a *branch to the quadrate lobe* and then, crossing the plane of the falciform ligament, divides into an *upper* and a *lower* branch to the left lobe.

The true plane of subdivision of the liver into equal halves is that demarcating the territories of the right and left Glissonian systems. This *principal plane*, first described by Rex (1888) and Cantlie (1898), is well to the right of the plane of the falciform ligament, and can be defined on the surface of the liver by injection of right and left hepatic ducts with different soluble dyes. These diffuse through to the surface in their separate areas. On the anterior aspect of the liver, the plane runs from the gall-bladder notch below to the origin of the central hepatic vein above. Behind, the boundary bisects the gall-bladder fossa and the caudate lobe. This plane is well defined, therefore, by obvious landmarks, and is of corresponding surgical importance. The central hepatic vein also lies in this plane.

All the liver between the principal plane and the plane of the falciform ligament is supplied by branches of the left Glissonian system, given off with rare exceptions to the right of the falciform ligament. Thus the classical *left lobe* has its own separate pedicle from both Glissonian and hepatic vein systems.

In the right half of the liver, the antero-medial and postero-lateral Glissonian branches define corresponding zones, but the boundary between them follows no precise anatomical landmarks, is variable in position, and lacks sharpness near its right extremity. Moreover, the right hepatic vein—contrary to Gans (1955*b*)—is not necessarily a guide to the position of the plane.

To summarize, the liver may be divided into right and left halves about the principal plane, or into right and left lobes by the plane of the falciform ligament. Further subdivision of the right half into antero-medial and postero-lateral zones is less justifiable.

In applying the anatomical findings to surgery, the first and most obvious consideration is that any incision of liver substance should if possible be made with the internal anatomy of the organ closely in mind. For example, a wedge removed from the upper part of the left lobe may interrupt the left hepatic vein in its oblique path downwards and to the left, and so jeopardize the viability of the rest of the left lobe.

As regards the removal of large sections of liver, use should be made of the fact that, there being few blood or biliary vessels crossing the plane of the falciform ligament, and practically none across the principal plane, these planes are relatively bloodless. Therefore we may consider right and left hemi-hepatectomy, and right and left lobectomy.

The further consideration arises that if the Glissonian and hepatic vein pedicles of an area can be secured at the beginning of the operation, a further reduction in the risk of serious hæmorrhage is achieved. *Formal hepatectomies* may be defined as satisfying this requirement. The only operations falling strictly into this category are those of right and left lobectomy, supplied each by a separate Glissonian pedicle, and the right by the right and central hepatic veins, the left by the left hepatic vein. The hemi-hepatectomies are not formal hepatectomies because, while the appropriate Glissonian pedicle can be secured, the central hepatic vein lies in the plane of section and cannot be tied without risk to the remaining half of the central segment of the liver.

Lesser hepatectomies than this have been described. For example, Gans advocates in cases of carcinoma of the gall-bladder a "middle lobectomy", that is the excision of the central hepatic vein segment between falciform ligament and the plane between antero-medial and postero-lateral zones of the right liver half. Patel and Couinaud (1955) mention excision of the lower half of the left lobe. But the indications for an excision of less than the whole of the left lobe must be few. Such operations depend more on the hæmostatic technique of the operator than upon a knowledge of the internal anatomy.

There is one application of left lobectomy deserving special mention. In cases of high obstruction of the common bile duct, Longmire and Sanford (1948) described cutting across the left lobe until a suitably dilated intrahepatic bile duct was found, excising the appropriate wedge of liver and anastomosing the cut end of the bile duct to jejunum. Dogliotti and Fogliati (1954) claimed to have used in 1946 a similar procedure with a left lobectomy as the primary step. This operation is anatomically sounder, and I think it should be commenced by blunt dissection from the region of the inferior end of the liver attachment of the falciform ligament, upwards along the fossa for the ligamentum venosum. In this region, or immediately to the right of the fossa, there runs the bile duct to the quadrate lobe. This duct, even in a normal post-mortem liver, can easily be found and is sometimes quite as large as the main ducts to the left lobe. It is quite possible that where the biliary tree was suffering from the effects of back-pressure this duct might itself be suitable for anastomosis with the jejunum. The operation would be technically simple provided the dangerous relationship of the blunt end of the left portal vein, lying superficial to the duct in the fossa at a distance never less than two inches from the inferior rim of the liver, were remembered. No harm would be done if the duct could not be found or were not large enough, because the dissection could be completed to remove the left lobe and a main duct used as Dogliotti described.

This work was carried out while acting as Research Assistant in the Department of Surgical Studies at the Middlesex Hospital, laboratory facilities having been provided at the Institute of Clinical Research.

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The Diagnosis of Acute Pancreatitis

By HENRY WAPSHAW, M.D., Ch.M., F.R.C.S.Ed.

WHEN confronted with a case of acute pancreatitis our responsibility is twofold. Firstly, we have to recognize the condition and secondly, try to identify the type. It is usual to think of two pathological types; the one presents as necrosis and hæmorrhages and the other as œdema or merely swelling or induration of the gland. The custom of referring to the latter as subacute pancreatitis is at times misleading since its clinical differentiation from the destructive form is not always easy in the initial stage. For the purpose of this paper both forms are classed as acute pancreatitis.

The more identifiable features of the disease will be described as they were found in 40 cases—the sum of my experience. There were 26 cases with gross lesions, of whom 12 died, and 14 mild cases with 1 death. The state of the pancreas was ascertained from the following sources: (*a*) autopsy, 7; (*b*) emergency laparotomy, 8; (*c*) delayed laparotomy, 17; (*d*) there remain 3 with large pseudo-cysts who were regarded as necrotic types and 5 with transient symptoms but diagnostic serum or urinary amylase readings who were regarded as benign types. Acute pancreatitis was suspected in only 50% of the series, hence the high operation rate.

Clinical Features

There were 28 females and 12 males and the ages ranged from 40–60 years. 15 patients had experienced *past episodes* of acute abdominal pain. How far these were related to the pancreas is uncertain, but one patient had five relapses and is fit and well to-day.

The *pain* in an established case is intense, gripping and often paroxysmal. It may come on abruptly or take hours to reach its height; it may pass off abruptly or linger as a dull ache; it continued for four weeks in one of the necrotic group. 7 patients were not relieved by morphine. Objective studies of pain are not altogether reliable, but one gained the impression that some of the benign group suffered as much as those with severe lesions, though for a shorter period as a rule. Then again some of the latter appeared to be so overcome that they could scarcely muster the effort to communicate their feelings. Possibly for this reason, two fulminating cases did not actually complain of any pain. They were exceptional in that they developed pancreatitis and died two and four days after operations on the stomach.

The pain commenced in the following parts: supra-umbilical area, 27 cases; right sub-costal, 4; left sub-costal, 4; left loin, 2; and thoraco-lumbar, 1. The pain passed through to the back in 50% of the series.

Sickness with vomiting occurred in 33 patients. Among those unaffected were the two post-operative cases mentioned. It was not so pronounced or lasting, though just as prevalent, in the benign group when compared with the grossly affected (*see* Table I). The main characteristic of the sickness seems to be its persistence even after the pain has gone.

Table I.—Summary of Clinical Findings

	Total series (40 cases)	Hæmorrhagic necrosis (26 cases)	Œdema or induration (14 cases)
Pain	38	24	14
Sickness ..	33	22	11
Cyanosis ..	9	5	4
Jaundice ..	12	6	6
Palpable mass..	10	10	—
Glycosuria ..	7	6	One known diabetic

Passing to the more *objective* features, the behaviour in bed varied widely from patient to patient. Some were restless, others lay with their knees drawn up, while others were apathetic, heavy-eyed, and seemingly oblivious to their surroundings. There was little distinctive about the temperature chart. Half of the patients were in a state of prostration during the first day or two but a gross fall in blood pressure was noted in a minority. Hypotension as a sign of pancreatitis is, I believe, over-stressed and its absence should not exclude the disease.

Cyanosis either confined to the lips or more widely distributed occurred early, and was present in 9 patients of whom 1 died. Its meaning was difficult to assess, but I surmise that these patients were unable to breathe properly owing to the pain. Discoloration of a more lasting nature at the umbilicus or loin, the signs of Cullen and Grey Turner, was absent throughout this series. A tinge of *jaundice* was observed in 10 patients and bile detected in the urine in 2 more. I explored the biliary tract in 8 of these at a quiescent period and in none were stones or other cause found. A likely explanation is compression of the bile duct as it ran behind the diseased pancreas (*see* Table I).

The areas of *maximum tenderness* were sited in the following places: supra-umbilical area, 16 cases; right sub-costal, 13; left sub-costal, 4, and left loin, 2. Muscular rigidity and distension were too vague for an accurate statement of their incidence.

A *mass* was felt in the upper abdomen in 10 patients. During the earlier stages this seems to be of the nature of a tangle of œdematous omentum and loops of bowel and later on due to a localized collection of fluid or pus. This sign was confined to the severe form (*see* Table I).

Albuminuria was a constant finding. *Glycosuria* was present in 7 cases, 2 of whom were known diabetics.

Table I lists the collective findings and shows how they were distributed in the two groups. Generally speaking, pain, sickness, cyanosis and jaundice were as prominent in the one group as in the other. Bearing in mind that almost half of the patients with necrosis died, the distinguishing features among the survivors were the longer spells of pain and sickness, the presence of a palpable mass, and glycosuria.

Diagnostic Methods

There are now several methods of detecting the characteristic enzyme response of acute pancreatitis but procedures do not concern us here. However, it is essential for diagnosis that samples of urine or blood for the amylase estimation should be taken within two days of the onset of symptoms.

The serum *amylase findings* in 14 of the series are presented in graphic form (*see* Fig. 1). Somogyi's method was used. They were serial observations and show how rapidly the elevated values return to normal levels. This rise in the amylase content of the blood or urine is not to be regarded as an index of the severity of the pancreatic lesion. What then does it indicate? The following experiment, which was designed to find out the effects of morphine on the serum amylase content, may help in elucidating the mechanism. As is well known, morphine stimulates the muscular tissue around the lower end of the bile duct to contract, thereby interrupting the flow of bile for periods of an hour or even longer. Fig. 2

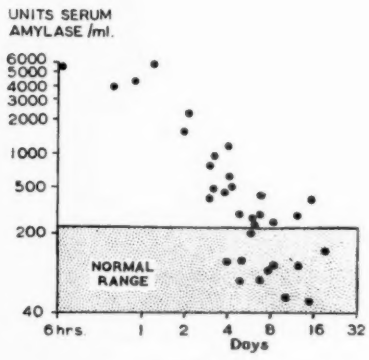


Fig. 1.

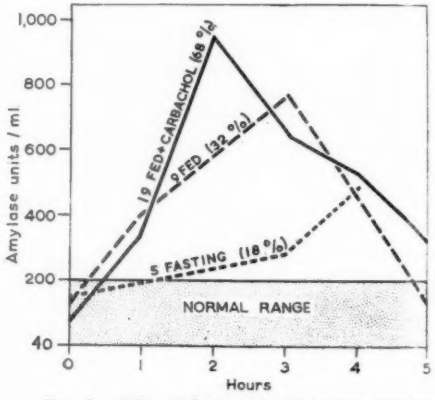


Fig. 2.—Effects of morphine on serum amylase in 84 normal persons.

furnishes evidence from the amylase content of the serum that the flow of the pancreatic secretion is likewise affected on occasion. 84 volunteers under experiment were divided into three groups of 28. Prior to receiving morphine the first fasted; the second received an ordinary three-course meal and the third had a similar meal plus carbachol (B.P.) intramuscularly (Wapshaw, 1953). The averages of those with raised readings in each of the three groups are presented. The numbers affected and the height of the response seemed to be proportional to the secretory activity of the gland and doubtless the duration of the obstruction resulting from the drug-induced spasm. I do not infer that an obstructive factor is the main case of acute pancreatitis but rather that the major ducts of the gland become secondarily occluded as a result of the distortion of its parenchyma. The above findings also indicate that the pancreas can be functionally deranged short of producing the clinical picture of acute pancreatitis, and thereby impugn to some extent the specificity of the amylase test as a diagnostic procedure.

However, the amylase findings are in most cases of pancreatitis dependable during the first twenty-four hours. By the end of the second or the third day they are apt to cause some doubts, especially when the question of a "missed" perforated peptic ulcer arises. Such cases, as is known, sometimes do have raised amylase readings, when the ferment lying free in the abdomen is particularly potent. Evidence of a continuous drop in the serum or urinary levels unassociated with air under the diaphragm helps to substantiate the correct diagnosis. There is little to choose between the urine or the serum as test fluids in performing the test. However, advanced renal disease may lead to inconsistencies, as illustrated by the case referred to in Table II. Note that the serum amylase values were raised well after the condition had settled, yet the urinary index was low. The persistently raised readings obtained in subsequent months confirmed the suspicion that here was an instance of faulty excretion of amylase from the blood as a result of renal failure.

There remain the *serum calcium* levels as an indication of the type of pancreatitis. In the hæmorrhagic form the presence of widespread fat necrosis imposes an excessive demand on the available calcium. For this reason there is in some cases a reduction in the serum calcium, which occurs around the third day and lasts a few days more.

TABLE II.—ACUTE PANCREATITIS: CHRONIC NEPHRITIS

H. C., female, 44 years

Duration of illness	Serum amylase Somogyi units/ml.	Urinary amylase Wohlgemuth units
10th day	1,180	
12th ,,	640	5
15th ,,	530	10
25th ,,	800	
	(Blood urea 166 mg.%)	
2nd month	800	
3rd ,,	400	
5th ,,	450	
7th ,,	200	

(Died two years later in uræmic coma, blood urea 213 mg.% after second attack of acute benign pancreatitis.)

SUMMARY

The pain and sickness are the most prominent symptoms. The relative inconspicuousness of the signs is itself suggestive of the disease. The points in favour of the destructive form as against the benign form are the prolongation of the symptoms, a palpable mass, glycosuria, and a drop in serum calcium. It cannot be over-emphasized that a high rise in the amylase content of the blood or urine during the first two days of illness is an invaluable diagnostic sign. Equivocal findings thereafter may still be shown to be appreciably raised by carrying out further tests.

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Unexpected Post-operative Bleeding Due to Hæmorrhagic Disease

By OWEN DANIEL, M.B., B.S., F.R.C.S., H. T. SWAN, M.B., Ch.B., M.R.C.P., and E. K. BLACKBURN, M.D., F.R.F.P.S.

The University Department of Surgery and the Department of Hæmatology, The Royal Infirmary, Sheffield

THE hæmorrhagic diseases in which trauma is likely to be followed by abnormal bleeding are usually easily recognized after simple clinical examination. Surgery is then undertaken only if absolutely essential and only after every possible step has been taken to minimize the expected blood loss (Macpherson and Learmonth, 1956).

The usual warning of the presence of a hæmorrhagic state is the development of episodes of excessive bleeding or bruising after minor injury, or of spontaneous hæmorrhage from the intestinal, genito-urinary or respiratory tract. Reports of similar conditions in blood relatives should also be taken seriously, and the presence of petechiæ, unexplained bruising, jaundice, a biliary fistula, splenomegaly, chronic anæmia or chronic diarrhœa must of course never be disregarded.

Occasionally surgery has to be performed on a patient suffering from a severe hæmorrhagic disorder which has produced no recognizable symptoms or signs before operation. We have recently met this complication after gastrectomy in a patient with chronic myeloid leukæmia (Blackburn and Daniel, 1957) and after open perineal biopsy for carcinoma of the prostate (Swan *et al.*, 1957). This experience has led us to review very briefly those conditions which may cause unexpected bleeding after operation.

Primary vascular abnormalities which lead to a hæmorrhagic state commonly present with purpura or bruising and as such are easily recognized, although sometimes these conditions come to light only during surgical operation. It is also possible for allergic purpura of the type usually associated with Henoch's name to present with abdominal pain, vomiting or intestinal bleeding and under these circumstances operation may be performed before other characteristic signs such as cutaneous and mucosal hæmorrhages appear (Wintrobe, 1956).

Hæmophilia and allied disorders are usually recognized before surgery is undertaken. Difficulty may, however, arise where there is no clear history of abnormal hæmorrhages since early childhood or relevant family history. This difficulty occurs most often in mild forms of hæmophilia or Christmas disease and these mild forms constitute an appreciable proportion of the total number of patients suffering from these diseases. In such cases a deep hæmorrhage may easily be mistaken for a suppurative condition and surgical drainage attempted with disastrous results.

During the last few years increasing attention has been given to the biological significance of fibrinolysis and acquired fibrinogen depletion. In the normal organism there appears to exist an equilibrium between the fibrin-producing process of blood coagulation and the fibrin-destroying properties of certain enzymes. Fibrinolytic enzymes and thromboplastins have been found in the blood and the tissues, especially the prostate, lungs and pregnant uterus. The release of abnormal quantities of these tissue enzymes has been reported as causing dangerous bleeding after operations on the prostate, extensive operations on or injuries to the lungs, premature separation of the placenta, amniotic embolism, and certain other obstetric complications (Astrup, 1956).

Increased fibrinolysis has been demonstrated in shocked states, in anxiety, after heavy muscular work, after the injection of adrenaline, and in certain immune reactions (Macfarlane and Biggs, 1946). The shock of severe surgical operation may thus induce a hæmorrhagic state. It has also been found that the administration of large quantities of stored blood in a relatively short period of time may lead to a platelet deficiency sufficient to interfere with blood coagulation (Krevans and Jackson, 1955). Here then are the possibilities of a dangerous vicious circle.

Carcinoma of the prostate can lead to a hæmorrhagic diathesis in many ways, such as through extensive invasion of the bone-marrow as well as through the production of circulating proteolytic enzymes (Prout *et al.*, 1956).

Abnormal proteolytic activity has also been reported in the plasma of two men undergoing prostatectomy for benign disease—both suffered severe post-operative bleeding and death resulted in one (Scott *et al.*, 1954).

It is clear that no surgical procedure should be performed on a patient with carcinoma of the prostate if there is evidence or even suspicion of a hæmorrhagic diathesis. As a first step œstrogens should be administered. If the cancer is sensitive to œstrogens the bleeding tendency will thereby be controlled.

If abnormal bleeding is encountered unexpectedly during the course of a surgical operation, the following procedures should be undertaken:

(1) Careful surgical hæmostasis.

(2) Restoration of blood volume by transfusion.

(3) Immediate laboratory investigations to determine the specific hæmatological defect or defects so that appropriate therapy can be started as soon as possible.

(4) If a fibrinogen deficiency can be demonstrated, fibrinogen should be given by intravenous injection. It should be noted that whole blood is almost valueless in the specific treatment of hypofibrinogenæmia, but if pure fibrinogen is not available concentrated plasma should be used instead.

(5) If the bleeding is associated with carcinoma of the prostate attempts should be made to suppress the tumour by œstrogens. Benefit has also been reported from the administration of cortisone and corticotrophin in patients in whom all other methods of treatment were of no avail (Stefanini *et al.*, 1953).

ACKNOWLEDGMENTS

We are grateful to the Board of Governors of the United Sheffield Hospitals for a grant through the Hæmatology Research Fund and for support from the Yorkshire Council of the British Empire Cancer Campaign.

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The following papers were also read:

Carcinoma of the Adrenal Cortex Without Endocrine Effects.—Mr. KENNETH F. WOOD.

Massive Thrombophlebitis.—Mr. B. N. CATCHPOLE. (*See Lancet*, 1957, i, 343.)

Clinical Section

President—Sir HENEAGE OGILVIE, K.B.E., D.M., M.Ch., F.R.C.S.

[*February* 8, 1957]

Pneumonectomy for Agenetic Lung.—M. C. WATERFALL, F.R.C.S.

In September 1954 a 45-year-old German woman, who had lived in England for twelve years, was admitted to Kingston Hospital with ten years' progressive breathlessness, cough with 3 oz. of purulent sputum daily, tiredness and headaches. When she had "pneumonia" at the age of 10 her doctor noticed her heart was "on the right side". During childhood she frequently had a productive cough.

On examination.—She was plump with second degree clubbing. The trachea was deviated to the right. There was flattening of the right side of the chest and the apex beat was palpable in the 5th right intercostal space. Heart sounds normal. The breath sounds were normal over the upper part of the right chest anteriorly and all over the left side. Posteriorly to the right of the spine there was loud bronchial breathing. Scattered rhonchi on both sides. She was producing 3 to 4 oz. of thick, green sputum daily.

Investigations.—Chest X-ray: Heart on the right, dense triangular opacity in the position of a collapsed middle and lower lobe.

Bronchoscopy: The carina was rotated clockwise. Thick pus welled up from the right lower lobe. A bronchogram confirmed there was distortion of the mediastinum and showed that the right lower lobe bronchus ended blindly (Fig. 1).



FIG. 1.—Bronchogram showing heart pulled over to the right and blind ending of right bronchial tree. Aerated lung in the right chest is part of left upper lobe.

Treatment.—November 1954 right pneumonectomy.

The left upper lobe had herniated across the mediastinum and filled the space normally occupied by the right upper lobe. The right lung was very small, solid and densely adherent to the diaphragm and chest wall. The pulmonary artery and veins were slightly smaller than usual and bronchial arteries large. The lung was removed and the bronchus closed with wire.

Convalescence was uneventful.

She is now very well, her exercise tolerance is much improved and she has no sputum.

This case illustrates the well-known fact that removal of non-aerating lung increases the exercise tolerance, as the airless tissue acts as a shunt. This woman was thought to have agenesis of the lung rather than an acquired condition as the calibre of the right main bronchus was normal.

Waldenström's Syndrome or Macroglobulinæmia.—D. W. Oxbrow, M.B., B.S. for S. Karani, M.B., B.S., M.R.C.P.).

Mr. B., aged 51, was admitted to hospital on 6.9.56 complaining of gradual impairment of sight for two to three years, which had become much worse in the previous two months. He also complained of three years' recurrent epistaxes which required hospital treatment, and severe bleeding from hæmorrhoids which had ceased after hæmorrhoidectomy twelve months previously. He had noticed gradually increasing weakness and shortness of breath on exertion for four to six months.

On examination.—He appeared to be moderately anæmic clinically, pulse 88, regular; blood pressure 145/105.

There was generalized glandular enlargement, but no enlargement of the liver or spleen. Examination of the fundi showed marked venous dilatation with numerous hæmorrhages. There was no exudate or papillœdema (Fig. 1).

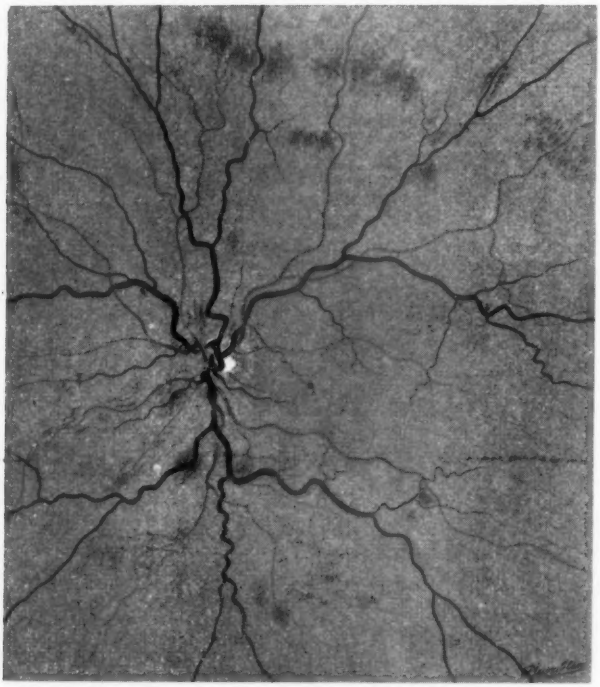


Fig. 1.—Fundi appearances showing venous dilatation and hæmorrhages.

Investigations.—Hb 23%. W.B.C. 5,000, varying from 4,000 to 7,000. Lymphocytes initially 40% rising to 50%. Platelets 43,000 initially, rising to 120,000. Occasional nucleated red cells and metamyelocytes.

23.1.57: Reticulocytes 3·7%. E.S.R. was barely recordable at 1 mm. in the first hour.

Serum proteins: Total 11·1, albumin 4·7, globulin 6·4 grams/100 ml., A/G ratio 0·73 : 1. The serum proteins rose to 13 grams/100 ml. of which 10 grams were globulin.

Electrophoresis showed the abnormal globulins to be entirely in the γ-globulin fraction.

Ultracentrifugation (Dr. A. S. McFarlane) showed that there were at least two macroglobulins of high molecular weight present in the serum.

Serum fibrinogen 120 mg./100 c.c.

Tests depending on abnormal globulins were as follows: Thymol turbidity 25 units. Thymol flocculation 5+ units. Colloidal gold 5+ units. Formol gel positive. Bleeding time: three minutes. Clotting time: eight and a half minutes. Examination for LE cells negative. Coombs test negative. Sternal marrow: Poorly cellular sample. 80–90% mature lymphocytes. Lymph gland biopsy: Proliferation of lymphocytes;

prominent sinuses filled with reticulum and inflammatory cells, with fibrosis of the hilum of the gland. Chest X-ray: Cardiac enlargement. Prominent vascular markings. X-ray of skeleton normal.

The patient developed a large right pulmonary infarct on the fifth day after admission to hospital, and subsequently a right pleural effusion, but since then he has slowly responded to repeated transfusions and prednisolone, with disappearance of retinal hæmorrhages and improvement of vision from 6/60 right 6/60 left, to 6/9 right and 6/24 left. He still has occasional mild epistaxes.

Discussion.—Jan Waldenström (1944) was the first to recognize this condition when he described two cases of essential hyperglobulinæmia with fibrinogenopenia. Ferriman and Anderson (1956) reported a case with identical signs and symptoms to those of Waldenström's original case and collected 16 other cases from the literature. They emphasized the characteristic features which may be observed in the fundi, namely venous dilatation with scattered hæmorrhages but without exudate or papillœdema.

The two diseases which may come into the differential diagnosis are multiple myeloma and chronic lymphatic leukæmia. In the former there is evidence of characteristic bone-marrow changes, a history of bone symptoms and characteristic X-ray appearances of the bones; in the latter the appearances of the bone-marrow, gland biopsy and the progress of the disease usually establish the diagnosis.

Some interesting features of this illness need further work to explain them. The excess of abnormal globulin appears to be related to the proliferation of lymphocytes and their metabolic breakdown. The bleeding may be explained by the lack of fibrinogen and platelets, and perhaps also by venous distension caused by unduly viscous blood. The anæmia may be the result of (*a*) blood loss, (*b*) interference with marrow function by lymphocytic replacement, (*c*) multiple thrombi resulting from the peripheral stasis caused by increased viscosity of the blood. These thrombi may account for the low platelet and fibrinogen figures and perhaps for the poor response to transfusions, e.g. 8 pints of blood given in ten days raised the patient's hæmoglobin by only 22% and 4 pints in five days by only 14%.

Treatment.—There is no satisfactory treatment. Blood transfusions produce only slight improvement in the blood picture and though cortisone may be used (as in this case) for its theoretical action in depressing lymphoid tissue there has been no good effect here either clinically or on the serum protein figures.

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Renal Failure Treated with Prednisolone.—J. E. LENNARD-JONES, M.B., M.R.C.P. (for RICHARD ASHER, M.D., F.R.C.P.).

History.—A boy, aged 16, was admitted to hospital on 23.12.56 complaining of swelling of his face, abdomen and legs. Three weeks previously a superficial skin graze became infected. A week later he began to feel unwell and ten days later puffiness was noted around his eyes. Subsequently his ankles, legs and abdomen became swollen. The patient himself had noted a gain of over 12 kg. in weight over the ten days before admission. There was no history of recent sore throat, of red urine or of renal pain. A routine urine test was normal two months previously.

Clinical findings.—Gross œdema of the face, body and legs. Pleural effusions. Ascites. Blood pressure 160/110. Throat normal. Healed abdominal skin graze.

Initial investigations.—Urine—gross albuminuria but no red blood cells or casts. Total serum protein—3·6 grams/100 ml. (Albumin 2·5 grams/100 ml.) Electrophoresis of serum proteins—α_2 and β-globulin raised, γ-globulin low. Protein content of œdema fluid—0·1 gram/100 ml. Blood urea—46 mg./100 ml. Serum cholesterol—512 mg./100 ml. Throat swab—scanty β-hæmolytic streptococci.

Course in hospital (*see* Fig. 1).—The acute onset of the illness, its possible relationship to streptococcal infection and the finding of hypertension suggested immediately a diagnosis of acute glomerulo-nephritis (Ellis Type I). However, the findings on investigation clearly pointed to a diagnosis of nephrosis.

In the hope that a spontaneous diuresis might occur the only measures adopted during the first three weeks after admission were fluid restriction, a largely carbohydrate diet and course of parenteral penicillin. During this time considerable anxiety was felt because increasing œdema caused breathlessness; hypertension and gross proteinuria persisted and the blood urea rose (highest 123 mg./100 ml.). The treatments available were limited

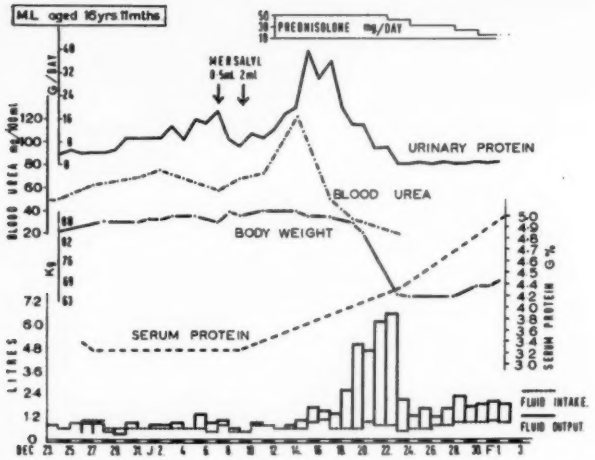


FIG. 1.—Showing the diuresis which occurred after treatment with prednisolone. The diuresis began before a fall in the urinary protein loss.

as mercurial diuretics were not effective, cation exchange resins appeared contra-indicated owing to the renal failure and the boy was too ill for malarial therapy. It was decided that prednisolone should be given and that acupuncture should be performed if this failed.

Three days after starting prednisolone a diuresis began which reached a climax between the seventh and the eleventh days when 23·4 litres (41 pints) of fluid were passed and the body weight fell 22 kg. The hypertension disappeared, the proteinuria lessened and the blood chemistry returned to normal. Prednisolone was gradually discontinued without increase of albuminuria or return of œdema.

Comment.—This case again demonstrates that a diuresis can occur before a fall in the urinary protein (Roscoe, 1956). The successful result of treatment with prednisolone despite gross œdema and a raised blood urea seems noteworthy. It is proposed that this boy should be maintained on small doses of prednisolone if gross proteinuria or œdema recur.

(We wish to thank Dr. D. J. Crockett for estimating the protein content of the œdema fluid.)

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ROSCOE, M. H. (1956) *Quart. J. Med.*, N.S., **25**, 353.

Dr. Richard Asher: This illness does not clearly resemble either Type 1 or Type 2 nephritis, but an intermediate condition. I showed this patient because I would like advice on the diagnosis and treatment. Could the nephritis be related to the infected abrasion three weeks previously? How long should one wait before giving cortisone? Is the dramatic response in this case attributable to its use? If so, how does it work and how long ought it to be continued? Has it any use in preventing recurrences?

The following cases were also shown:

Neurofibroma of Lung. ? Collagen Disease.—Dr. M. P. SCOTT (for Dr. GERALD SLOT).

Calcified Cyst in Abdomen. ? Hydatid.—Dr. D. GORDON and Mr. G. QVIST.

Congenital Gigantism of Right Forearm and Hand Due to a Hæmangioma.—Mr. J. E. H. PENDOWER (for Mr. N. C. TANNER).

Tuberculous Right Kidney Presenting as a Perinephric Abscess.—Dr. J. MORAN (for Miss M. C. WATERFALL).

Myelomatosis with Xanthomatosis.—Dr. J. E. LENNARD-JONES (for Dr. RICHARD ASHER).

Pretibial Myxœdema and Latent Lymphatic Leukæmia.—Dr. B. D. HOLTON (for Dr. T. PARKINSON).

Otitic Hydrocephalus.—Dr. JOHN H. BURKINSHAW.

JOINT MEETING No. 2

Section of Otology with Section of General Practice

Chairman—PHILIP J. JORY, D.S.O., F.R.C.S.
(President of the Section of Otology)

[*February* 1, 1957]

DISCUSSION ON RECURRENT OTITIS MEDIA IN CHILDREN

Mr. Lionel Taylor: Otitis media in children is a complication of upper respiratory infection. The onset is usually abrupt with pain and raised temperature, but otitis media may arise insidiously. In the untreated and uncomplicated child the drum will rupture by pressure necrosis within hours and the pain at once be relieved, or a minor infection settle without rupture. When antibiotics are exhibited for a full five days the intratympanic effusion will slowly subside as the infection is combated and the fluid drain away through the eustachian tube or be reabsorbed in the ear and mastoid cell system. A certain amount of residuum will remain, forming fibrosis, and therefore hearing will not return to "normal" for three to four weeks or longer. There may be some permanent impairment in hearing especially if attacks are repeated. If a myringotomy is done under general anæsthetic before the drum ruptures, pain will be at once relieved and the linear incision will heal far more quickly than the circular hiatus left by necrosis; the contained fluids will escape completely and hearing will return to normal very quickly. Resolution will be hastened by use of antibiotics in adequate dosage after myringotomy, supported by decongestive nasal drops and aural toilet. Causes of recurrent otitis media may be listed as shown in Table I.

TABLE I.—CAUSES OF RECURRENT OTITIS MEDIA IN CHILDREN

1. Eruption of teeth.
2. Enlarged adenoids.
3. Persistent perforation of tympanic membrane.
4. Latent mastoid infection.
5. Lymphoid hyperplasia.
6. Idiopathic.

Teeth.—The relationship between teething and otitis media is undisputed but the mechanics of this are not proven. Presumably there is reflex congestion of the middle ear which allows pooling of mucus in the tympanum. This may become infected from the blood stream if the child catches a cold. Treatment of the otitis media is as outlined earlier.

Adenoids.—Where there are large adenoids these, when infected, will swell up and obstruct the pharyngeal end of the eustachian tube. Stagnation of mucus occurs with subsequent infection either directly from the nasopharynx or by the blood stream, resulting in otitis media. When the otitis media recurs with every severe cold, removal of adenoids is indicated. Between attacks these children will have intact tympanic membranes but these are usually indrawn. They also have symptoms of enlarged adenoids such as mouth breathing and snoring. In a well-judged case no further otitis media occurs with subsequent colds. It is often convenient to remove the tonsils at the same operation where there has been any history of tonsillitis, although the tonsils have no direct bearing on the otitis media. These children often have an associated maxillary antritis which clears up after removal of adenoids unless there is an additional vasomotor rhinitis.

Perforation.—The majority of ruptured tympanic membranes heal, but a few remain with a perforation. This does not necessarily affect the hearing, but such a perforation remains a potential source of danger. If, for instance, water gets into the external meatus from under-water swimming or vigorous hair washing, it may enter the middle ear. If it does so, otitis media will follow. Similar effects will be produced by syringing such an ear for removal of wax. Until recently there was no satisfactory treatment for this condition, but now the operation of myringoplasty will prove of value for some of these cases.

Latent infection.—Where inadequate dosage of antibiotics is used, particularly where the drum has not ruptured, latent infection may persist. After a time of apparent normality the otitis media will flare up again within two to four weeks, or may present as mastoiditis, or one of its complications. One such boy of 7 complained two weeks after treatment of seeing two television screens. He was admitted to hospital and found to have papilloedema. The only aural sign was reddening of the deep meatus in the attic region and some deafness, but at operation the mastoid cell system was full of cheesy granulations and he had a sterile lateral sinus thrombosis. His hearing returned to within normal limits two months later. A second child presented with vomiting and other signs of meningism. His aural sepsis was minimal, but the cell system was completely disorganized. Lumbar puncture in each child showed the pressure to be raised but culture was sterile confirming a diagnosis of otitic hydrocephalus. Again after a simple Schwartz mastoidectomy, recovery was complete and uncomplicated and hearing became normal.

Hyperplasia.—Removal of adenoids, especially in the very young, may be followed by diffuse lymphoid hyperplasia of the nasopharynx. The pharyngeal end of the eustachian tube contains lymphoid tissue. Usually this causes little trouble but in these children hypertrophy may be responsible for recurrent obstruction with resultant otitis media. This cannot be removed successfully by surgery, but responds on occasion to radiotherapy.

Idiopathic group.—Finally there remains a group of children in whom otitis media recurs with monotonous regularity despite every treatment. These patients, whose otitis media must be labelled idiopathic, remain one of the unsolved otological problems. Such children have clear nasal airways between attacks, with no symptoms of enlarged adenoids or sinusitis. Ear drums are of normal lustre and are not indrawn. Between attacks Rinne's test is positive and Weber's central. Possibly the eustachian tubes are more widely open than normal, allowing muco-pus to gravitate up the tube in sleep against the ciliary stream, or very rarely it is possible that such children have had their adenoids removed and at that time the eustachian cushions were damaged by the curette.

Both the lymphoid hyperplasia group and the idiopathic group will start a steady improvement about the age of 14. If masterly inactivity has been possible up to that time the reward will now be gained in that the attacks will cease as the lymphoid tissues regress and assume adult form.

Dr. I. Friedmann: The role of the clinical pathologist in the management of otitis media depends, to a certain extent, on the general practitioner and surgeon. The surgeon may feel less inclined to ask the clinical pathologist too many questions. The general practitioner has also adopted a more active attitude when using the antibiotics as it can be unwise to delay treatment until the results of the laboratory tests are to hand.

The value of the sensitivity test cannot be doubted but its results are not immediately available. This is due to the practical difficulties and to the considerable amount of work involved. In addition, it has become increasingly difficult to keep abreast of developments in this field. Several new antibiotics have been introduced recently and our personal laboratory experience of them has so far been limited.

Besides a critical attitude of mind the interpretation of such information presupposes a knowledge of the bacteriology and pathology of a given disease. The fact is sometimes overlooked that treatment with antibiotics does not represent treatment of a disease, as does surgical treatment, but is directed against the causative organisms. It is not entirely correct to talk of the antibiotic treatment of otitis media. It would be more accurate to refer to the treatment of e.g. staphylococcal, pneumococcal, &c., infections of the middle ear.

The best assistance the clinical pathologist can give is based on the long-term study of the bacteriology, histopathology and experimental pathology of otitis media.

TABLE I.—BACTERIOLOGY OF ACUTE OTITIS MEDIA IN 2,441 PATIENTS
(Overall incidence of micro-organisms in 1952–56)

	Number of strains: 3,391	%
Staphylococcus pyogenes	1,022	(41·8)
Staphylococcus pyogenes penicillin resistant	411	(16·8)
Streptococcus pyogenes	669	(27·4)
Streptococcus viridans	157	(10·6)
Streptococcus pneumoniæ	103	
E. coli	103	(4·2)
B. proteus	157	(6·4)
Ps. pyocyanea	136	(5·5)
Mixed	285	(11·7)
No growth	348	(14·2)

The overall incidence of the predominant organisms has not varied greatly in the years

1951 to 1956 (Table I). Gram-positive cocci have predominated and have on the whole remained sensitive to penicillin. There were no penicillin-resistant strains among the 669 strains of *Streptococcus pyogenes*, isolated from 27·4% of all patients.

The overall incidence of *Streptococcus pneumoniæ* and *viridans* has remained low (Friedmann, 1952). Type 3 pneumococci, though frequently encountered, appeared to have no untoward effect on the course of acute otitis media. In 1956 about 30% of our pneumococci belonged to type 3.

The overall incidence of *penicillin-resistant* strains of *Staphylococcus pyogenes* was 16·8%. 4·18% of all staphylococci showed *in vitro* resistance to ten units of penicillin. These figures have remained remarkable steady in our hospital.

Contrary to the experience in other fields there has emerged no clinical or pathological evidence which might incriminate the penicillin-resistant *Staphylococcus pyogenes*. There has been no evidence of a change in the clinical picture of acute otitis media and the number of otogenic intracerebral complications has remained negligible. Moreover, clinical experience shows that patients with acute otitis media harbouring penicillin-resistant staphylococci may respond favourably to penicillin treatment.

In the writer's opinion penicillin has remained the antibiotic of choice in the treatment of acute otitis media.

TABLE II.—BACTERIOLOGY OF RECURRENT OTITIS MEDIA IN 917 PATIENTS
(Overall incidence of micro organisms, 1952–56)

	Number of strains, 1,030	%
Staphylococcus pyogenes	267	(29·1)
Staphylococcus pyogenes penicillin resistant	162	(17·6)
Streptococcus pyogenes	195	(21·2)
Streptococcus viridans	53	(11·1)
Streptococcus pneumoniæ	49	
E. coli	51	(5·6)
B. proteus	80	(8·7)
Ps. pyocyanea	67	(7·3)
Mixed	93	(10·1)
No growth	13	(1·4)

The present writer has defined a recurrence of otitis media as the recurrence of an acute infection after a symptom-free interval of an arbitrary period of six months. As the figures indicate, the overall bacteriology is similar to that found in acute otitis media (Table II). It is interesting to note that the number of negative cultures was lowest in this group.

TABLE III.—BACTERIOLOGY OF CHRONIC OTITIS MEDIA IN 1,700 PATIENTS
(Overall incidence of micro organisms, 1952–56)

	Number of strains: 2,067	%
Staphylococcus pyogenes	539	(31·7)
Staphylococcus pyogenes penicillin resistant	219	(12·9)
Streptococcus pyogenes	119	(7·0)
Streptococcus viridans	57	(4·6)
Streptococcus pneumoniæ	21	
E. coli	138	(8·1)
B. proteus	432	(25·4)
Ps. pyocyanea	218	(12·8)
Mixed	143	(8·4)
No growth	181	(10·6)

The shift towards a predominance of Gram-negative bacilli is characteristic of the bacteriology of chronic otitis media. There are several efficient antibiotics against the majority of the Gram-negative organisms. The majority of organisms of *E. coli* type, *A. aerogenes* and *Klebsiella pneumoniæ* (Friedlander's bacillus) have shown *in vitro* sensitivity to streptomycin, chloramphenicol and tetracycline. *Ps. pyocyanea* was usually sensitive to polymyxin B; *B. proteus* was sensitive to streptomycin and chloramphenicol.

The management of chronic otitis media is largely surgical owing to the irreversible changes of bone and mucosa.

The histopathology of otitis media.—One of the objects of the present investigation was to try and solve the question as to whether the pathology of otitis media or mastoiditis has changed since the advent of the antibiotics, a change often suggested. For this purpose bone chips removed at recent mastoidectomy operations have been dissected and examined, and the pathology of experimentally induced otitis media in the

guinea-pig studied. It has been pointed out in previous reports (Friedmann, 1955*a* and *b*; 1956) that there was no microscopical evidence to suggest a fundamental change in the pathology of otitis media.

[Slides illustrating the irreversible bone and mucosal changes, with particular reference to the significance of epidermoid cholesteatoma and cholesterol granuloma were shown.]

Antibiotic treatment of experimental otitis.—The injection of various organisms, such as *Ps. pyocyanea*, *Streptococcus pneumoniæ* and *B. proteus*, into the middle-ear cavities of the guinea-pig produces otitis media (Friedmann, 1955*a* and *b*).

The experiment to be described was carried out with a strain of *Streptococcus pneumoniæ* (Type 3) isolated from a case of acute otitis media. This strain spread regularly from the infected to the non-infected ear of the animal causing bilateral chronic otitis media. Guinea-pigs were divided into four groups. After the intra-aural injection of a suspension of the organism, Group 1 was kept as untreated controls; Group 2 was treated immediately with terramycin for intramuscular injections, giving 50,000 units daily for six days. Group 3 was treated in the same way but only after seven days following infection and Group 4 a fortnight after infection.

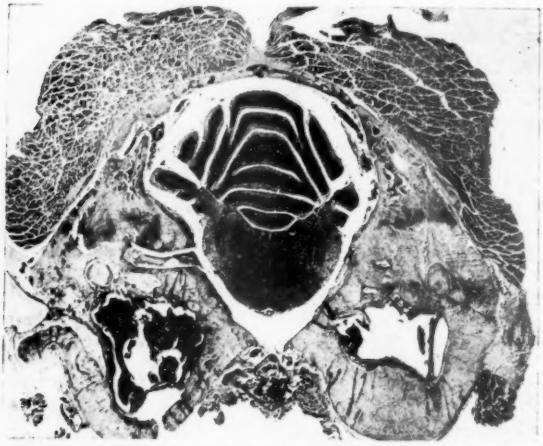


FIG. 1.—Non-treated control animal showing bilateral chronic otitis media sacrificed six months after right intra-aural infection with *Streptococcus pneumoniæ*. ×3. H. and E. G.P. 389.

Result.—All animals survived and were killed six months after infection. The control animals in Group 1 developed bilateral chronic otitis media leading to a great deal of suppuration and bone formation in both ears (Fig. 1). In Group 2 the infection remained localized in the infected ear causing only some thickening of the bulla and slight suppuration (Fig. 2). *In Group 3 the infection appeared to be completely cured.* There was no evidence of infection in either ear (Fig. 3). In Group 4 the infection, although prevented from spreading to the non-infected ear, caused chronic otitis media in the infected ear (Fig. 4).

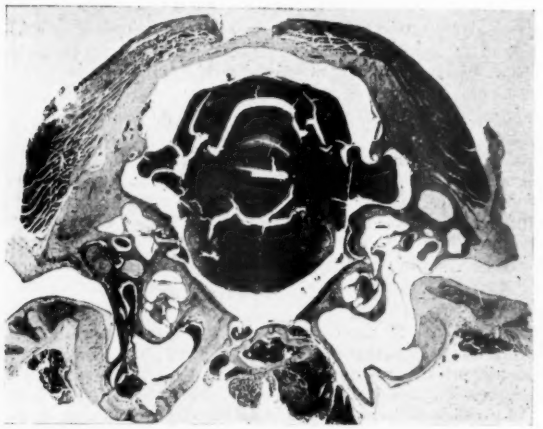


FIG. 2.—Animal treated with terramycin immediately after right intra-aural infection with *Streptococcus pneumoniæ* and sacrificed after six months. Moderate otitis media in infected ear; non-infected ear healthy. ×3. H. and E. G.P. 391.

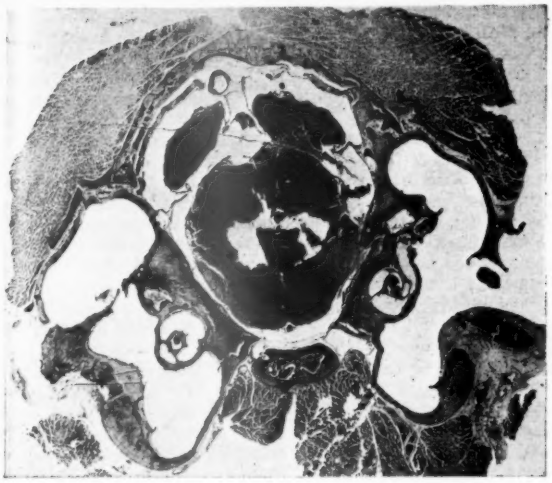


FIG. 3.—Treatment delayed until seven days after infection. Animal sacrificed after six months. There is *no evidence of otitis media* in the infected (or non-infected) ear. ×3. H. and E. G.P. 397.



FIG. 4.—Treatment delayed until fourteen days after infection. Animal sacrificed after six months. The infected ear shows fully developed chronic otitis media but the infection was prevented from spreading to the non-infected ear. ×3. H. and E. G.P. 401.

I cannot offer an entirely satisfactory explanation of these results; but the experimental evidence appears to confirm the clinical experience that there is a time for antibiotic treatment of otitis media, as there is a time for surgery.

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—— (1955*a*) *J. Laryng.*, **69**, 27.
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Dr. G. F. Abercrombie: Between 1924 and 1934 I attended 82 patients who had between them 115 attacks of otitis, of which 35 were bilateral, giving 150 drumheads for observation. Of these, 80 resolved without complication: in 25, the drumhead perforated with 19 recoveries, 3 secondary myringotomies and 3 mastoid operations; in 45, primary myringotomy was done with 37 recoveries and 8 subsequent mastoid operations. At the end of this series, no case of acute otitis media had been allowed to become chronic and no patient was left with a

running ear. Of the 82 patients, 10 came to a mastoid operation, and 12%, or something near it, was the common finding of those days.

Then, as now, in two attacks out of three, an antecedent infection in the nasopharynx was to be recognized—a respiratory catarrh, cough or cold; sore throat or tonsillitis; whooping cough, measles, scarlet fever or diphtheria. Dentition also was listed as a predisposing cause, but in the great majority the otitis was simply the result of a common cold. In about one patient in three, both ears were affected, and in half of these patients, the second ear was affected on the same day as the first.

The signs and symptoms of acute otitis media are pain, fever and an inflamed drum. Deafness is often present, perhaps always so, but is difficult to assess in young children. Earache is the constant symptom; it may last only half an hour or it may keep a child awake all night. There is often some tenderness on pressure over MacEwen's triangle or over the tip of the mastoid process—signals for prompt action. More than half of all my cases subsided and resolved with symptomatic treatment only. In many patients, however, the drum ruptured spontaneously. When it is recollected that frank pus always drained from these ears, it must be admitted that the end-results were remarkably good, for only 12% required a mastoid operation. In an endeavour to improve upon this figure the E.N.T. men of the day demanded that the tympanic cavity should be drained in the early stage by myringotomy. I strove to follow this advice and made great efforts to get these drums incised as soon as they began to bulge, but the results were not encouraging. In my series, primary myringotomy was performed 45 times, 30% of all cases, but the operation, in specialist hands, failed to prevent disease of the mastoid on 8 occasions, and the percentage of success, 37 out of 45, 82%, was certainly no better than that obtained by nature's second method of cure, namely, perforation.

The results to-day show an enormous improvement. Assuredly, acute otitis media is still with us. Logan (1953), analysing the clinical records of eight practices, with something over 27,000 patients at risk from April 1951 to March 1952, found that it was diagnosed in about 3% of that population, but that mastoiditis was mentioned in only 1 in 60 of that 3%. Recent surveys from general practice, particularly that conducted by the Medical Research Council in 1955, show that, although the condition is just as common as formerly, myringotomy is no longer done and a mastoid operation is very seldom required. The incidence of acute otitis media rises up to the age of 5 or 6 years and then falls sharply. 80% of patients nowadays receive sulphonamides or antibiotics in some form—oral, parenteral or local—and residual defects are neither frequent nor serious.

There remain at the present time two questions of very great interest and practical importance. First, what is the explanation of the astonishing improvement in the prognosis for a child who is the subject of acute otitis media? It appears that almost every second child suffers from this disease in early life, and yet myringotomy and mastoidectomy are exceedingly rare. Mastoiditis, like puerperal fever, seems to be a thing of the past. I believe that this remarkable change is to be attributed solely to modern therapy, now so very extensively used. Secondly, what change occurs at the age of 6 years, which cuts the incidence of otitis media by half? Whatever it is, it enables those of us in general practice to continue with confidence to reassure anxious parents that their children will "grow out of it".

REFERENCE

LOGAN, W. P. D. (1953) *Stud. med. Popul. Subj.*, No. 7. H.M.S.O.

Dr. David Wheatley: The advent of the antibiotic era has transformed acute otitis media almost overnight from a surgical to a medical condition. At the present time it is mainly treated by the general practitioner. My remarks reflect, therefore, my own views and experience of this condition as I have encountered it under general practice conditions.

The main object of treatment in general practice is to annihilate the infection at the earliest possible moment, thereby allowing the natural processes of resolution to occur unhindered. In the unperforated case, appropriate antibacterial treatment causes such rapid subsidence of inflammation that myringotomy is seldom, if ever, necessary. Often, however, perforation has already occurred before one is called to the case. Nevertheless I have not yet seen a case in which the ear drum has failed to heal and I see some 50 to 100 cases in a year. I have not in any of my cases had a myringotomy performed and in ten years of practice I have not encountered a case of mastoiditis.

The object of antibacterial treatment is simple, but the means of achieving it has been vastly complicated by the glittering array of antibiotics available today. Antibiotics, and I here include the sulphonamides, at the present time may be divided conveniently into three groups. We are not much concerned with the third group, for the main use of these antibiotics is anti-staphylococcal. In general practice we encounter mainly the domesticated strain of staphylococcus and not the wild variant of Fairbrother (1956)

which seems so to infest the wards of our hospitals. The great majority of domiciliary staphylococcal infections remain sensitive to penicillin.

1. Narrow spectrum ..	sulphonamides penicillin streptomycin
2. Broad spectrum ..	chloramphenicol tetracyclines
3. Penicillin substitutes	Erythromycin Spiramycin ("Rovamycin") Novobiocin ("Albamycin") Oleandomycin

In general practice, therapy is blind as indeed it must always be unless perforation has already occurred. Since the infection may be due to a variety of organisms and indeed is often mixed, it is better to cover as wide an antibacterial field as possible. For this purpose I would advocate the synergistic combination of penicillin and a sulphonamide. By this means penicillin is virtually converted into a broad-spectrum antibiotic, yet at the same time retaining its unique bactericidal action, which still excels that of any other antibiotic. The broad-spectrum antibiotics, with their disadvantageous side-reactions and high cost, may then be held in reserve for the rare case that fails to respond to the primary treatment.

I consider that oral penicillin combined with a sulphonamide, provided it is given in high enough dosage, is entirely adequate in this condition (Wheatley, 1953). This is particularly so in general practice as one is dealing mainly with children. It is important to present the patient with a dosage regime that is likely to be adhered to in the home; for we are entirely dependent on our patients for the correct timing of doses. One cannot rely on patients with what is to them a non-serious illness, taking nocturnal doses. Very often also they will not admit to failing to conform to the instructions given them. As a result treatments may be condemned as failures when in fact they were not given a chance. It is only occasionally that the discovery of a half-full bottle of tablets by the bedside, when it should have been an empty one, gives us a clue as to the real cause of failure.

Therefore I give my drugs eight-hourly, a regime which conveniently fits in with the patient's daily routine. This allows doses to be taken on awaking, in mid-afternoon and on going to bed. I have found that this is usually adhered to. As regards dosage, my standard dose for an adult is: penicillin G 500 mg. (800,000 units) (or penicillin V in half this dose) +1 gramme of sulphadimidine, eight-hourly. Children are dosed in proportion and advantage may be taken of the many pleasantly flavoured liquid preparations available.

I last collected my results in 1952, when in a series of 100 cases the following data were obtained (Wheatley, 1952*a*):

TABLE I.—OTITIS MEDIA.

No. of cases	100
Infection subsided	100
Chloramphenicol substituted for oral penicillin+sulphadimidine ..	3
Recurrence in three months	3
Recurrence at longer intervals*	7
Hearing—whisper at 15 ft.+ (follow-up 6–9 years)	100

*Subsequently prevented by removal of T's and A's.

Since then results have been so uniformly similar and satisfactory that I have not needed to record them further.

In chronic otitis media we can enlist the aid of the bacteriologist in determining bacterial species and sensitivities. Nevertheless specific antibiotic treatment is often disappointing, since elimination of one organism so often results in its replacement with another different one. Obviously other factors are concerned and our knowledge of these is obscure. I would like to consider two possibilities, allergy and inflammation.

A persistent discharge after antibiotic treatment, particularly if it is serous in nature and shows only low-grade infection on culture, may be a manifestation of an allergic reaction to the original infection. On this hypothesis it would be reasonable to treat such cases with either antihistamines or steroid hormones. The latter having the advantage of reducing inflammation and making any residual organisms more accessible to a further antibiotic onslaught.

I have in the past given antihistamines both locally and orally to such cases, with some successes (Wheatley, 1952*b*). During the course of such treatment, 3 cases with a persistent

discharge due to Proteus became sterile and I was stimulated to investigate the antibacterial properties of the antihistamine used ("antistin") *in vitro*, with the following results:

TABLE II.—ACTION OF "ANTISTIN" (½%) ON PROTEUS (+ = GROWTH, − = BACTERIOSTASIS)

Time in hours	Dilutions 0	1 : 2	1 : 4	1 : 8	Control culture Nothing added	Control culture Sterile water added
¼	+	+	+	+	+	+
1	±	+	+	+	+	+
4	−	−	+	+	+	+
8	−	−	±	+	+	+
18	−	−	±	±	+	+

Despite this effect, however, the treatment failed to eradicate Proteus in subsequent cases and I have not pursued this line of investigation. Recently I have had some better success with the local application of hydrocortisone and hydrocortisone+neomycin drops.

Nevertheless chronic otitis media remains a fairly difficult problem in general practice where lack of time and facilities contribute to a need for some fairly simple home therapy.

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WHEATLEY, D. (1952*a*) *Med. ill.*, **6**, 443.
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Mr. S. R. Mawson referred to the possible importance of teething as an ætiological factor when it occurred concurrently with an infection of the middle ear.

Most textbooks had little to say on this but in Wilson's recent book "Diseases of the Ear, Nose and Throat in Children," the opinion was given that the connexion between teething and otitis media was "merely an ignorant superstition". Was this true?

In hospitals, infants were seen with acute or recurrent otitis media in whom it appeared that the only concomitant with any possible ætiological significance was the eruption of teeth.

He had collected 32 cases—admittedly a small series, but in these he was sure that there was no other precipitating cause. Each seemed to be a primary otitis media associated solely with erupting teeth. In December last he sent a questionnaire to the mothers of these children inquiring whether there had been any subsequent earache or discharge and if so what was considered to be the cause. 15 had replied, but in only 2 had there been any subsequent earache and discharge and both had been attributed to severe colds, so that 13 out of 15 had had no further trouble with the ears since that connected with teething. The period of follow-up ranged from half to two and a half years after the cessation of teething and it seemed significant that in this period 86% were free from ear symptoms. In his own experience, he would say that teething undoubtedly did involve some infants and children in otitis media. While the exact mechanism had yet to be explained, there would still seem to be a sound position to defend against the extreme charge of "ignorant superstition". As to treatment, he felt that each one needed to be treated as otitis media on its own clinical merits.

Mr. A. G. Tresidder spoke in defence of the operation of myringotomy which was used before the advent of antibiotics when dealing with the case of a child with a red bulging drum. True, the operation did not always prevent a subsequent mastoid operation. Nowadays, such a condition of the middle ear was almost universally treated by antibiotics and in a large number of cases the bulging and redness disappeared and apparently the hearing was restored, but it had been suggested that the absorption of the exudate in the middle ear led to some fibrosis round the ossicles and might be a cause of deafness in after years. He felt himself that when one was confronted with a red bulging drum myringotomy should be carried out to see what the organism was and the appropriate antibiotic given.

Dr. L. Roodyn discussed recurrent otitis media associated with enlarged adenoids which was a particularly common condition in children between 5 and 7 years of age. Recurrent hæmolytic streptococcal infection of the throat with spread to the middle ear accounted for some of the cases, but a greater number were probably caused by virus infections. At the Meeting on Adenoviruses of the Pathology and Epidemiology Sections held on January 15, 1957 (in press), Dr. H. Pereira of the Common Cold Research Unit, Salisbury, described a small outbreak of these infections which occurred in the families of some of the laboratory workers. One of the boys who was about 5 years of age had a typical adenovirus infection and some four or five months later his adenoids were removed. It was possible to cultivate from the adenoid tissue removed at operation the same type of virus.

This observation which showed that the adenoviruses persisted in the adenoid tissue for several months, suggested that the overgrowth of this tissue may represent a hypertrophic reaction of the lymphoid tissue to the continued presence of the virus.

The recurrent otitis media was probably caused by the mechanical effects of a pad of hypertrophied adenoid tissue or perhaps there might be direct infection of the middle ear by the adenovirus.

Whether the removal of the adenoids significantly reduces the recurrence rate of otitis media is still undecided.

Mr. S. W. Allinson said that there should be a prophylactic approach to diseases of the ear, nose and throat. The baby should be taught to breathe through the nose with the mouth shut. The mother should press up baby's chin to close the mouth and so encourage breathing through the nose. The nose should only be blown gently and never pinched.

If, in later life, a patient should be seen complaining of attacks of otitis media then in the first place breathing through the nose with the mouth shut should be taught and the nose should only be blown gently.

If these methods fail it may be necessary to remove the tonsils and adenoids but this operation should rarely be necessary in the first instance.

Dr. G. O. Barber said that he was interested, when Mr. Lionel Taylor was going through his causes of otitis media, that there should be no mention of the significant number connected with the onset of measles. Twenty-five years ago an attack of measles was very often coincident with an attack of otitis media and he wondered why they did not think of it nowadays as such an inevitable complication. Had something happened to measles to prevent this complication? Had a social change taken place with regard to measles? Twenty-five years ago quarantine was extremely strict and everything was tried, to postpone the onset of the exanthem until the patient was older and had gone to a residential school.

He was reminded of 1935 when out of a possible 340 boys there were 96 cases of measles of whom 76 were in the sanatorium at once, and it was a sanatorium designed to hold a maximum of 56 cases which meant that it was grossly overcrowded. At the same time there was a virulent hæmolytic streptococcus in the school causing sore throat and out of the 76 cases 40 developed acute otitis media.

Like Dr. Abercrombie in those days he too was under the influence of the myringotomist and he and his partner used to go along the moment a boy reported earache, and perform a myringotomy. They did 40 myringotomies and there were four mastoids; this was the same percentage as Dr. Abercrombie's.

In the follow-up of these boys, the majority had a second or even a third attack during their three or four years at school. The acute attack during measles seemed to establish a tendency to recurrent otitis media.

The **Chairman** said that he thought the virulence had decreased in scarlet fever as well as in measles. One used to find that the drum head went in a few days, one never saw that nowadays. He was surprised at the number of people who had had measles before they went to school, did Dr. Barber say that 3% had not had it?

Dr. Barber said that nowadays the majority of the boys in the senior school had had it, 3% of boys had not had measles.

Mr. F. C. W. Capps said he could remember as a young patient in the pre-antibiotic days having to wait a week for the drum to burst; and if ever the antibiotics or the sulphonamides failed in efficiency he hoped that the general practitioners would remember that myringotomy was still a very good procedure. It was a good rule "where there is pus let it out", especially in the presence of pain.

Mr. G. H. Bateman said that the main indication for myringotomy was pain which was not relieved quickly by antibiotics.

Mr. J. F. Lipscomb made the point that general practitioners should test the patient's hearing and not rely on purely clinical symptoms. One has often to do a myringotomy two to three weeks after the initial attack of otitis media because of persistent deafness.

Dr. R. Goulding said that the previous speakers' questions as to the general use of antibiotics were important. They had heard from the general practitioners present what they did and how they did it, but he would point out that those who had come to the meeting were the enlightened ones. He had done a number of locums and had come to the conclusion that a vast quantity of antibiotics used for otitis media was ineffective because the routes of administration and the doses employed were neither appropriate nor adequate. He was beginning to wonder whether this great improvement in the course of otitis media over the last ten or fifteen years was due to antibiotics or whether it was due to a change in the natural history of the disease. Although it would take a great deal of courage, it would be interesting

to study two parallel series of patients, one given antibiotics and the other treated by conservative methods alone, and see just how much difference there would be in the results.

Dr. L. W. Batten said that with regard to myringotomy he would like to agree with Dr. Abercrombie that early incision was bad, one should wait until pus was present. It did not relieve pain very often and certainly did not stop pus forming. It was good sense to let the pus out, but nowadays it was not often there.

Mr. J. W. S. Lindahl said that otologists in the hospital saw the patient once and not always again, and it was sometimes difficult to assess the effect of removal of adenoids on recurrent otitis media. It seemed that by the removal of adenoids the process of recovery was initiated and that the cause of recurrence was not only obstruction but some degree of infection of this eustachian tube and surrounding tissues.

Frequently there would be another attack or two of otitis media after the operation and he warned mothers that they might expect this. He could produce no figures at all, but it was his impression that the number of attacks of otitis media after operation were almost in proportion to the number of attacks before. There was a hard core of cases which went on and on but there was also a majority who got better and one did not necessarily know about them as they were not always brought up again.

Mr. Lionel Taylor, in reply, said that there were three points; the first one was Dr. Barber's mention of measles. His table showed the causes of *recurrent* otitis media but he agreed that measles was a predisposing cause of acute otitis media. Secondly, his impression was, in spite of what Mr. Lindahl said, that generally if the adenoids were adequately removed—he used that word advisedly—the fall in the incidence of otitis media was most marked. He had seen it in his own family and probably all of them had seen it in theirs.

He thought Dr. Roodyn was a little unlucky in some of his cases, he might have had a larger number than average of the "hard core" children who went on getting otitis media.

The third point was Mr. Tresidder's—what one did when one was faced with a red bulging drum? As Mr. Capps had said, with a general anæsthetic and a myringotomy the result was dramatic and the course of the illness was shortened very considerably. Having done a myringotomy the progress of the infection was apparent. One had only to look and could then see if there was any more pus coming out and one knew that the child would not develop a latent mastoiditis. If the child was given penicillin, however adequate the dose, there was a chance that he would develop one of those rare mastoids and mastoidectomy would have to be done.

Dr. D. Wheatley said he was a little disturbed by the speaker who said he had to wait for his drum to perforate, that might have happened years ago but if he went to his general practitioner nowadays he would be treated with antibiotics and the infection would be gone long before the week was out. Those who stressed the diminishing virulence of the streptococcus for the improvement of results really did not believe what they said! An admission had been made that few would be prepared to put up a control series with and without antibiotics.

The Chairman said that as a result of the discussion he remained convinced of the potency of antibiotics in ear disease but he was also convinced that adequate doses must be given.

Section of Otology

[*March* 1, 1957]

The following papers were read:

Some Points on the Technique of Temporal Bone Surgery (with colour slides).—Mr. Terence Cawthorne.

Bilateral Hearing Improvement Following Fenestration.—Mr. C. A. Hutchinson.

Myringotomy Restated.—Mr. R. J. Martin.

Habilitation of the Deaf.—Mr. I. G. Robin.

Bleeding from the Ear in Closed Head Injuries.—Mr. P. V. Wadsworth.

Post-traumatic Conduction Deafness.—Mr. I. B. Thorburn.

Malformations of the Auricle.—Mr. W. O. Lodge.

Amnion Graft in Radical Mastoidectomy.—Mr. L. Taylor.

The papers were discussed by **Mr. W. H. B. Magauran, Mr. H. V. Forster, Mr. G. I. Bateman, Mr. I. Simson Hall, Mr. P. E. Roland, Mr. W. S. McKenzie, Mr. H. D. Brown Kell, Mr. P. Scott, Mr. S. W. G. Hargrove, Mr. G. Thompson, Mr. Miles Foxen, Mr. G. A. Fraser, Mr. B. S. Carter, Mr. E. G. Collins and the President.**

The meeting will be published in the *Journal of Laryngology*.

Section of General Practice

President—JOHN H. HUNT, M.A., D.M.

[*December* 19, 1956]

DISCUSSION ON THE AFTERMATH OF HYSTERECTOMY AND OOPHORECTOMY

Dr. Katharina Dalton: Not all hysterectomies end in tragedy, but a great deal can be learnt from those which do. The sooner the after-effects of this radical operation are fully understood the more will the importance be realized of considering every possible alternative treatment before the final decision to perform a hysterectomy is reached. To study the long-term effects of this operation a questionnaire was used to follow up all cases in my practice. This practice is not representative of general practice, but is overloaded with sufferers from premenstrual syndrome and menopausal disorders. It is, therefore, not possible to compare this series with controls and no claim is made in this respect. In this series, of the 43 women 6 were single and 3 widowed. Of the 34 married women 3 have since obtained divorces and a further 12 have sought the advice of a marriage guidance counsellor in an effort to prevent marital disruption. Thus in 44% of married women in this series hysterectomy has been followed by marked loss of marital happiness. Undoubtedly in many cases marital discord may have been evident before hysterectomy, but this vital event in the lives of a married couple may possibly prove the last straw. The husband, who cannot and knows he never will be able to enjoy sexual satisfaction with his marriage partner, has a greater temptation to seek the company of another woman. Nevertheless the marriage may have been on an even keel prior to hysterectomy.

The three divorced women all reported normal intercourse before operation, but intercourse had not been attempted since. Before operation 76% of the married women experienced normal intercourse, and the remainder reported unsatisfactory intercourse due to dyspareunia or infrequency. However, after the operation only 22% reported normal intercourse, 36% reported unsatisfactory intercourse and in the remaining 42% there had been complete abstention. This question was often answered by a look of surprise or such statements as "I didn't know I could" or "I thought I was all sewn up". One replied "Oh no, my husband is too thoughtful", but alas! one year later the thoughtful husband was enjoying the company of his secretary. Surely there is a failure here in pre-operative preparation and post-operative guidance in omitting discussion on this very important subject with husband and wife.

When asked if they were pleased with the result of the operation 23 of 43 women replied "No". Some amplified their statement with such remarks as "I feel pain more now", "I worry over trifles", "Never really well", "Don't like company", "It made me hard", "I always wanted children" or even "I've a lovely scar, but my health has never been the same since". In contrast the reason given by those who were satisfied was always the same "No worries about becoming pregnant". This suggests an insufficient knowledge of contraceptive measures and possibly too little faith in them, or that while believing it is morally wrong to use contraceptives, they are conscience free if gynæcologists render them permanently sterile.

Analysis of those who were satisfied with hysterectomy showed that they were equally shared among the married, single and widowed, but there was a marked difference in satisfaction according to the time that had elapsed since the operation. Thus, less than one year after operation 83% were satisfied, but between one and five years only 41% were

satisfied. The figure dropped to 33% for those six to ten years, and rose to 50% after ten years. These figures may account for the impression among gynæcologists that their operation has been successful, for they often see the patient for a final examination two to six months after leaving hospital, at a time when she is still happy with her recovery from a major operation but before she has returned to the full stresses and strains of everyday life, and before intercourse has been seriously attempted.

The age of the patient at the time of hysterectomy appears to affect the success of the operation. Of those who were under 40 at the time of operation 70% were satisfied, between 41 and 45 years only 43% were satisfied, dropping to 25% for those between 46 and 50, and 40% between 50 and 55 years. It is only those over 55 who give the pleasing figure of 100% satisfied with the result of the operation. This suggests that Nature objects most to interference by hysterectomy when this is performed at the time of the natural menopause.

Analysis of the extent of the operation revealed that 55% of those who underwent simple hysterectomy were satisfied, 50% of those who had hysterectomy with removal of one ovary were satisfied, but only 20% of those who underwent hysterectomy with bilateral oophorectomy were satisfied. This confirms the recognized teaching that the ovaries should be preserved if at all possible. Only two women underwent subtotal hysterectomy, so no comparative figures for this and total hysterectomy can be given.

Was the incidence of neurosis high after hysterectomy? 74% of the women were troubled by recurrent headaches. In half of these women headaches had been noted to occur premenstrually before operation, but the post-hysterectomy headaches were increased in intensity, often accompanied by vomiting, photophobia or blurred vision. Vertigo was a recurrent symptom in 60%, hot flushes occurred in 68%, rheumatism in 50%, lethargy in 57% and depression in 62%. Thus the presence of six common neurotic symptoms occurred in over half the women. Charts of some members of this series showed how these neurotic symptoms recurred cyclically at the time of the menstrual equivalent (Fig. 1).

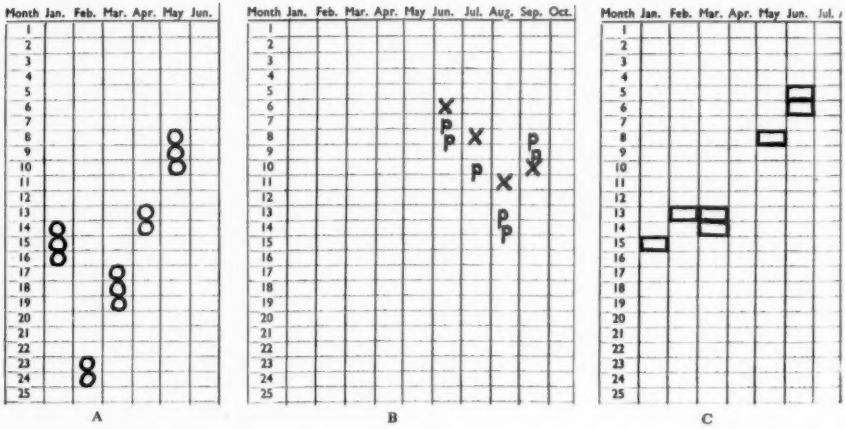


FIG. 1.—A, Patient aged 50, para-1; hysterectomy for fibroids at the age of 45. ○ = headache. B, Patient aged 48, single; hysterectomy and bilateral oophorectomy at age 45. X = giddy; p = abdominal pain. C, Patient aged 47, para 5; hysterectomy five years ago for menorrhagia. Bilious attacks occurred with periods. ▭ = bilious attacks.

Headaches and vertigo occurred at twenty-four to thirty days' interval and were accompanied by lethargy, depression and tension. Fortunately these cases of cyclically recurring symptoms respond excellently to progesterone or ethisterone, and in this series 22 women were so treated. The dosage of progesterone required to render these patients symptom-free is on the whole higher than among normal sufferers from premenstrual syndrome. One professional woman with heavy responsibilities is to-day leading a life filled with social engagements on a dose of 75 mg. progesterone daily; previously she was afflicted with migraine and depression and lived only for the day when she could retire at 55 years

and spend her whole day resting. Hot flushes are recognized as a menopausal symptom which responds to œstrogen therapy, and again, the late Dr. Joan Malleson (1955) reminds us that relatively large doses of even synthetic œstrogen preparations may be needed to correct the hormone balance. In the light of these facts it would appear that these multiple symptoms are due to endocrine imbalance rather than neurosis.

Excessive weight gain is another troublesome symptom. In this series 50% noted a gain of 1 stone within a year of operation, and 35% noted a gain of 2 or more stones within this space of time. Increases of 3, 4, and even of 5 stones during the first post-operative year were recorded. An acute weight gain occurs during the first two or three months and is followed by a gradual but persistent rise. The obesity is chiefly of the water retention type responding rapidly to fluid and salt restriction, diuretics and dieting. This regime should be instituted as soon as post-operative weight increase is recorded. Green-Armytage's (1955) advice is for a low fat diet following hysterectomy as "the incidence of coronary atherosclerosis in castrated females approximates that in males, a ratio normally in the region of one in ten".

For what reasons was hysterectomy performed? Or, more important, could hysterectomy have been avoided? This series undoubtedly included a few examples where this operation could have been avoided, or should have been the last resort after other methods of treatment had failed. The causes in this series were fibroids 17, menorrhagia 14, ovarian cyst 9, endometriosis 4, missed abortion 3, post-menopausal bleeding (Stilbœstrol) 2. Multiple causes were noted in 5 cases. The fibroid was an accidental finding in 4 cases, while attending for infertility 3 and for contraceptive advice 1. In exactly half the cases of menorrhagia no alternative treatment had been tried or suggested. There are occasions where hysterectomy is undertaken because of a low hæmoglobin, but iron deficiency anæmia due to malnutrition can, and does, occur in menopausal women as well as in other ages. Nor must it be forgotten that a lay person, who has only seen her own individual menstrual loss, is often unsure how to answer the question "Are your periods heavy?" To enquire into the amount of sanitary towels used is fallacious, merely giving an index of the fastidiousness of the patient. It is the degree of soaking of sanitary towels which is significant, and in these days of cheap polythene bags it should be possible to inspect personally all towels used in cases of suspected menorrhagia. A plea is also made for the more universal use of menstrual charts to verify the patient's statement as to duration of loss and length of cycle. Nor should a single hæmoglobin estimation suffice for the diagnosis of anæmia due to menorrhagia. Indeed, the hæmoglobin may be down premenstrually, due to water retention causing hæmodilution, and rise after menstruation. Water retention can be demonstrated by weight gain, and this premenstrual water retention will respond to the use of diuretics and progesterone (Fig. 2). Can one justify a diagnosis due to blood loss if the anæmia improves after the blood loss?

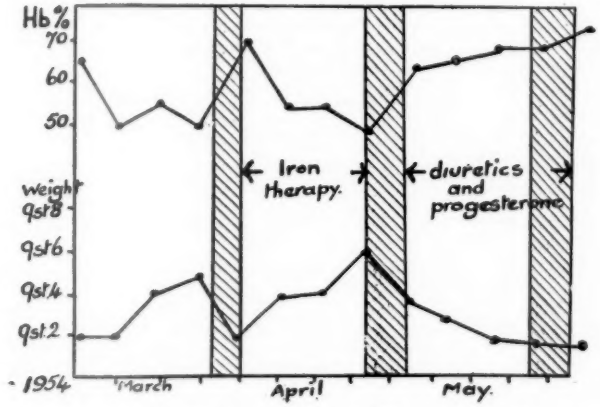


FIG. 2.—Aged 42 years. Para 6. ▨ = menstruation.

Can the aftermaths of hysterectomy be avoided? It is suggested that if their presence is

anticipated and appreciated then they can be avoided. There should be a careful selection of cases by attempts at alternative treatments. It is for the gynæcologist to decide in individual cases whether radiotherapy could be a possible alternative. Myomectomy still has a place in surgery. Curettage should not be forgotten. Hormone therapy and psychotherapy also have their uses. Utriculoplasty is of interest. This consists of resection of a portion of the uterus; uterine function is maintained and bleeding is reduced as the area of the endometrium is reduced.

When the decision to perform a hysterectomy is reached the pros and cons of the operation should be impartially presented to both husband and wife. The patient should know which symptoms she may expect to be alleviated by this operation. Floodings will cease; dysmenorrhœa will go; sterilization will be permanent. Headaches, depression and other accompaniments of menstruation will continue to occur cyclically; hot flushes will become more acute. There may be a weight gain of 1 or 2 stones within a year. Dyspareunia will not improve, but hysterectomy may be a convenient excuse for total abstention.

Post-operatively the path of the artificial menopause will be eased by discussion and simple psychotherapy, while the alleviation of unpleasant symptoms with hormones may be necessary. The weight gain should be noted, and, when required, advice on dieting given. The reference of patients after hysterectomy to an endocrinologist for observation is worthy of consideration. But primarily, let us recognize that there are aftermaths and that prevention is always better than the cure.

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Dr. G. J. V. Crosby: I have recently been considering some of the disturbing effects of oophorectomy in a short sequence of patients observed in my own practice. My indignation reached its acme, when I listened to the history of a single woman of 52 living alone. In 1934, at the age of 30, this patient complained of irregular and profuse bleeding suggestive of uterine fibroids and this diagnosis was ultimately made. At the time, she was engaged to be married and all seemed "set fair". The implications of operation were put to her and to her fiancé and it was pointed out that she might well have to lose her uterus, though nothing seems to have been said about removal of the ovaries. At operation, the fibroid uterus was completely removed. Her ovaries were considered suspect and bilateral complete removal was performed. The histological report was to the effect that there was no sign of malignancy.

We all of us appreciate the physical and the psychological phenomena of the natural climacteric. Perhaps it is not so usual to recognize the devastating impact of an acute onset of menopausal symptoms in a woman below 45 years of age; symptoms which we know to be directly attributable to an endocrine imbalance due to loss of ovarian hormones. This leads to uncontrolled and increased secretion of the gonadotrophic hormones which are thought to be the cause of flushing, sweating, increase of weight and ultimately hyperthyroidism and hyperadrenalæmia (hypertension and hirsutism).

The group of symptoms directly attributable to loss of œstrogens and resulting in vulval and vaginal atrophy, take longer to make themselves felt, but pruritus vulvæ and dyspareunia can be particularly distressing. These are probably more easily controlled by the administration of ovarian hormone, especially œstrogen. In the "classical" case which I am describing, there was apparently a rapid appearance of symptoms which not only made life thoroughly uncomfortable, but which also induced a psychological disorganization exhibited by bad-temper, irritability, loss of sexual interest and libido; and this, in spite of regular administration of œstrogens—in those days in the shape of monthly courses of Menformon, the dose of which is unfortunately not recorded. The engagement was ultimately called off; alcohol was taken in toxic quantities with all the significant and depressing results to be expected therefrom, and a promising happy life was utterly broken.

The effects of oophorectomy are not entirely reversible by hormone therapy and there may be some danger that this is overlooked when removal of the ovaries has to be considered. Therefore, every step should be taken to save as much ovarian tissue as possible, even to the extent of submitting the patient to a second operation (the first being a simple biopsy)—a procedure which may at the time seem drastic if not unjustifiable. I

understand that the small warty excrescences ("papillomata") so often seen on ovaries of normal or near-normal size are seldom, if ever, malignant.

In the United States two very long series have been analysed during the past six years. Doyle (1952) investigated a list of 546 patients from whom as many as 704 normal ovaries had been removed. Of these victims, only 5·1% were found to be carcinomatous. 56·8% had fibroids, 20·5% cystic ovaries, 8% so-called endometriosis and the remaining had lost their ovaries for reasons ranging from ectopic pregnancy to dysmenorrhœa and functional bleeding.

The total ablation of the ovaries must be followed by the disabilities of a natural menopause, but these are always intensified and more distressing the younger the patient. It is only too easy to assume that, in these days of hormone substitution therapy, the easy course of bilateral extirpation may be adopted without serious results. This is always a fallacious assumption and it is the general practitioner who sees the proof; but as general practitioners, the treatment of these symptoms by the administration of hormones is our responsibility. The symptoms must be divided into two classes: (1) those due to loss of the œstrogenic substance, including pruritus, dyspareunia, kraurosis and (when the uterus is retained) vaginal discharge and irregular bleeding; and (2) those due to hyperfunction of the anterior lobe of the pituitary, including flushing, sweating, and obesity—with the more distant possible effects of hyperthyroidism and hyperadrenalæmia. Obviously, the first of these groups requires the exhibition of œstrogens (and personally I like ethinyl œstradiol in small doses) while the second class demands the addition of testosterone which, I believe, the endocrinologists claim has a "braking" effect on the anterior pituitary. I might here mention a recent case, a woman of 42 who has had bilateral oophorectomy for carcinoma, but who has retained her uterus because there were abdominal deposits which made hysterectomy useless. Her most trying complaint has been that of vaginal discharge. Testosterone has had absolutely no effect upon this, though her other symptoms have recently improved. In view of the malignancy, administration of œstrogens has been discouraged, but I feel that otherwise this would probably be the rational approach.

Obesity may well yield to dietetic measures and in this it is, I think, strictly comparable with the obesity of the normal climacteric. In the same way, water retention and migraine probably demand progesterone plus salt and fluid restriction.

Unilateral ablation and even partial removal may be performed with far greater facility than that of total extirpation—for a cyst, for painful ovary (possibly simulating appendicitis, when both appendix and ovary may be improperly removed), for an ectopic pregnancy, in fact for a large variety of reasons. Even here we should press for the most extreme degree of conservatism which is safe and possible. It seems to be generally accepted that as long as some ovarian tissue remains, all will be well; I am not so sure. I recently saw a woman of 35 whose gain in weight following a simple unilateral oophorectomy for a small cyst was quite unbelievable—well over 30 lb. in just over a year. At the same time, menstruation had become irregular. Béclère and le Corvaisier (1953) suggest that the initial general reduction of ovarian secretion stimulates the pituitary to excessive gonadotropic hormone production with ultimate œstrogenic hyperfunction of the remaining ovary. This combined pituitary and ovarian action might well produce a syndrome such as I have described. The patient, in this case, is taking off some weight by diet alone. I suppose the administration of testosterone or progesterone would be the next rational step, but I doubt their clinical value. In this I find myself in agreement with Bishop (1956) who has largely discounted the importance of glandular substitution in the treatment of obesity generally—including that associated with the menopause.

Even unilateral oophorectomy may have a profound psychological effect. Knowledge of interference in any shape or form with the ovaries may well produce a fear of sterility. As a case in point, a woman of 34, recently married, in possession of the left ovary only, failed to become pregnant at as early a date as seemed desirable to her and her husband. A search for a cause for this assumed sterility was instituted, with negative results up to the time of a salpingogram which showed the left tube to be blocked and the right tube patent. These findings caused extreme despondency, the patient coming to regard herself as no longer of any use as a woman. However, continued effort has resulted in pregnancy and the fact that only one ovary is available is now forgotten.

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Mr. John Beattie: Gynæcologists are still divided on the subject of removal of healthy ovaries when a hysterectomy for innocent conditions is performed at the age of 40 and onwards. Although removal of both ovaries during pelvic surgery in women over 40 would save a few cases of carcinoma developing later on, the disadvantages of castration in these cases are enormous and I am emphatically in favour of preserving ovarian function whenever possible and at least up to the age of 50 or over. Richards (1951) and Barcroft-Livingston (1954) have shown by different methods that if a hysterectomy is done with preservation of the ovaries by a careful technique, menopausal symptoms need not occur for a long time afterwards and in some cases a normal menopause occurs years later. It is most important to preserve the ovarian blood supply and not to drag the ovarian pedicles into the centre of the pelvis with a purse-string suture. Figures show that removal of both ovaries before the age of 45 produces hot flushes in 98% of cases. This figure is reduced to 52% when one ovary has been removed and to 27% when both are retained.

Hysterectomy should always be total unless there are complications present which make a subtotal operation safer. The subtotal operation has an aftermath of its own. If carcinoma develops in the cervix after subtotal hysterectomy it is difficult to deal with. A multiparous cervix is often infected or eroded and discharge continues after a subtotal operation. Cervical polypi may arise in the cervical canal and cause bleeding and discharge. The aftermath of total hysterectomy is as follows: (1) The occurrence of dyspareunia if the vagina has been shortened. (2) The development of granulations at the vault of the vagina which produce bleeding and discharge, especially after coitus. The treatment is by one or more applications of silver nitrate to the area. (3) A patient who develops vaginal prolapse after total hysterectomy may require a special operation to cure this and to support the vaginal vault. (4) Occasionally a patient complains that loss of the cervix has affected her libido during coitus but an assurance that a possible cancer-bearing area has been removed should be enough to satisfy her.

Hysterectomy is now more often advised than some years ago because: (1) An artificial menopause produced by X-rays or the insertion of radium into the uterus does not protect the uterus from the development of carcinoma later on. (2) A patient who bleeds excessively at the menopausal age is often suffering from an endometrial hyperplasia, and if this is present carcinoma of the body of the uterus is more likely to develop in later life. (3) An irradiation menopause as an alternative to hysterectomy may lead to the sudden onset of hot flushes and other symptoms which may be severe and prolonged. (4) Despite intensive research on hormone therapy in relation to irregular menopausal bleeding, the results are extremely disappointing in patients who are in the late 40's.

It is essential when a hysterectomy is advised to spend some time explaining in detail to the patient and her relatives: (1) what the sex glands are in relation to the uterus; (2) that the uterus only has two functions, i.e. for the purpose of childbirth and if fertilization does not occur to cast off the lining each month; (3) that intercourse will proceed as before; (4) that the patient should have the same sexual feelings as before.

Removal of the uterus in certain circumstances can have a most fundamental and deleterious effect upon a woman. This particularly applies to the patient who is nulliparous or unmarried at whatever age the operation becomes essential. The effects are likely to be more serious if hysterectomy becomes necessary in the 30–40 age group but may also be profound even in the late 40's. The serious psychic consequences occur because a woman has been deprived of her capacity to bear children even if there has been no opportunity of doing so in the past and even if the woman has reached an age when childbearing is impossible. This feeling of potential capacity for childbearing does play an immensely important part in a woman's life.

The ill-chosen case and the hysterectomy performed without every effort being made to avoid the operation if possible may well lead to a mental upset which varies widely in type from a mild neurotic state characterized by anxiety and depression to hypochondriasis with aches and pains, and fears about the body, accompanied by severe depression.

There is a particular complication associated with hysterectomy which seems to have been unrecognized previously. Dr. Ida MacAlpine (personal communication) found that women complaining of intractable pruritus vulvæ, alone or in combination with pruritus ani, almost invariably revealed a history related to accidents in childbearing, such as miscarriage and stillbirth or to abdominal operations including hysterectomy. In over 80 cases thus investigated during psychotherapy these factors played a far more important part than lack of sexual satisfaction, to which pruritus vulvæ is commonly attributed. In 28 cases of most severe pruritus vulvæ a hysterectomy had been performed in 7 (25%).

There is no doubt at all that hysterectomy with conservation of the ovaries when carried out for the relief of severe symptoms untreatable by other methods is a great success. If the patient is in the fourth decade of life, is well adjusted but greatly inconvenienced by her symptoms she will welcome the removal of the uterus. It is important to be extremely conservative in the younger age group and avoid hysterectomy unless it becomes absolutely necessary. Hormone therapy should be persevered with in cases of functional uterine bleeding, myomectomy should be done for fibromyomata whenever possible, and conservative surgery adopted for the treatment of endometriosis.

The aftermath of oophorectomy.—Conservative ovarian surgery in the childbearing period of life is essential. Even in the late 30's and early 40's removal of both ovaries is a disastrous step. Only in the case of malignant disease should this be done. In cases of endometriosis and inflammatory disease in the pelvis, if operation is essential, as much ovarian tissue as possible should be preserved.

At the natural menopause about 75% of women will have some, if minor, symptoms but less than one-third of these will require œstrogen therapy. A much higher incidence of menopausal symptoms will follow removal of the ovaries or a castration dose of X-rays or radium before the natural menopause has occurred. These symptoms will be much less severe in the energetic and active extrovert who has never had time to dread the change of life and who may even look forward to the cessation of menstruation. The opposite to this is the woman who dreads the menopause as the end of everything. Such patients will be irritable and suffer in an exaggerated form from the fear of growing old, from a contracting social circle and from the death of relatives and friends, the children growing up and leaving home; there may also be anxiety over the economic background to their lives. All these troubles can be analysed and controlled by the stable and intelligent woman but they assume overpowering proportions in the unstable person. The main symptoms of an exaggerated menopause comprise the sympathetic storms of hot flushes and perspiration, the amenorrhœa and the atrophy of the genital organs. This triad may produce a severe psychological upset if the woman who is growing old does not develop fresh interests. She feels she is no longer attractive, the best of life is over, tension and anxiety develop and fear aggravates the autonomic instability of the menopause. With this dysfunction of the mind and body, obesity, peripheral pain, hypertension and osteoporosis may develop.

Before œstrogens were used in clinical medicine women who had menopausal symptoms were treated with bromides and valerian or small doses of phenobarbitone, and sooner or later the hot flushes and sweats were relieved. Œstrogens are not always entirely successful in curing patients of menopausal symptoms. It is most important to administer œstrogens in cyclical doses and never continuously and an effort should be made to find the minimum dose which will relieve the symptoms.

Bilateral oophorectomy is being done in increasing numbers for cases of carcinoma of the breast, relying upon the fact that a certain number of such carcinomas are hormone-dependent. Menopausal symptoms following this treatment are better alleviated by the male hormone than by œstrogens.

The use of a combined dose of œstrogen and androgen is often advocated as the two probably have a synergistic effect in controlling secretion from the pituitary and the androgen may act as a deterrent to the possible carcinogenic action of unbalanced œstrogens. The doses suggested are ethinyl œstradiol 0·01 mg. and methyltestosterone 5 mg. to be given in a cyclical manner.

Weight reduction is important from both the psychological and physical point of view and in this small doses of thyroid will be of help in the hypothyroid patient. A reduction in fluids and salt intake often helps to lessen the retention of fluid which may occur in the early days of the menopause and when œstrogens are being administered.

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Mr. Aleck Bourne was surprised to hear of the large number of serious disabilities which followed hysterectomy, as reported by Dr. Dalton. He has always regarded the operation, when performed for adequate indications and with conservation of the ovaries, as one of the most successful in surgery for restoring a woman's health. He emphatically endorsed

the opinion of Dr. George Crosby on the malign effects of removal of both ovaries before the age of 45, or even later, where there was no destruction thereof by serious inflammatory or malignant disease. Enucleation of simple cysts and dermoids was nearly always possible with retention of normal ovarian tissue.

Professor W. C. W. Nixon emphasized the importance of conservative surgery in gynæcological conditions. He agreed with Dr. Dalton that even after a hysterectomy, with conservation of the ovaries, psychological disturbance of varying degrees of severity might follow. A recent anatomical investigation by a Swedish gynæcologist had shown that the ovaries in a number of patients receive their blood supply mainly from the uterine artery. Thus a hysterectomy in such patients might interfere with the blood supply to the ovaries and ovarian atrophy would follow. He reminded the meeting of the success that Mr. Aleck Bourne had had in the operation of utriculoplasty for the treatment of menorrhagia of emotional origin.

Mr. Frank Musgrove said that when the operation of hysterectomy and oophorectomy was contemplated, the gynæcologist, whenever possible, should interview both husband and wife together pre-operatively.

At this interview, he should point out what the operation entailed, viz. an absence of the menstrual period and the onset of symptoms of the menopause, at the same time explaining that marital relationship should not be interfered with and that the effect of the loss of the ovaries can be replaced by oral administration of specific hormones.

In the summary of investigations and treatment sent to each general practitioner on the discharge of the patient, advice should be given that œstrogen-substitution therapy should be prescribed for all patients, in definite courses, for a period of at least six months, provided that malignancy has been excluded.

In following up several hundred cases of hysterectomy and oophorectomy, it was noted that in only 2% of cases was post-operative œstrogen-substitution therapy given by the general practitioner concerned.

Dr. E. Robert Rees completely disagreed with the very tragic picture that had been presented by the opening speaker. Were this a true reflection of the effect of hysterectomy, surely it would long ago have become a terrifying prospect to anyone. He firmly believed that these dreadful consequences could be prevented. It was insufficient merely to tell the patient that she would not be affected by this operation; it was essential that she be convinced of the truth of this. He adopted the attitude that unlike other forms of surgery, the patient losing a uterus, loses something that is not essential to her day-to-day metabolism or other body processes—unlike those others who have to lose their gall-bladder or some other essential structure.

He then pointed out to them that coitus in the common domestic animal was chemically controlled and therefore confined to ovulation times. This was not so in the human where the emotional factor was all-important. He pointed out to them that coitus took place during the early months of pregnancy in about 70% and usually continued after the menopause when the uterus ceased to be an actively functioning organ. These arguments nearly always succeeded in convincing the patient that the uterus was merely a box where a new lining was prepared each month and that when it caused distress or discomfort, its removal resulted in relief, with no disadvantages.

In conclusion, he stressed that it was the gynæcologist's duty not only to give the reasons for hysterectomy but also to make it quite clear to the patient that there should be no dreadful consequences from this operation. And he added that it was equally easily understandable that such consequences could and did result if the patient was not convinced to the contrary.

Dr. A. R. L. Abel drew attention to the possibility of using male hormone in cases of secondary carcinoma of the mammæ in very much larger doses than had been mentioned. It was not always possible to tell which cases were going to be suitable for such treatment, but laboratory tests were now being evolved which would show exactly in whom some improvement could be expected, and doses of up to 1,000 mg. of testosterone might be given with most startling and satisfying regression of secondary deposits in a very few cases.

BOOK REVIEWS

The Sexual, Marital and Family Relationships of the English Woman. By Eustace Chesser, M.D., in collaboration with Joan Maizels, Leonard Jones, B.Sc., Ph.D., and Brian Emmett, B.Sc. (Pp. xxxvi + 642; illustrated with many tables and charts. 75s. 0d.) London: Hutchinson's Medical Publications. 1956.

This monumental tome, referred to on the dust cover as "The Chesser Report" and running to 642 pages, is a statistical survey of the replies given by 6,500 married and single women to a questionnaire distributed more or less at random by 1,500 family doctors. It is, in effect, an English version of the earlier American Kinsey Report though it does not slavishly follow its predecessor.

The aims of the survey, as given by the authors, were (1) to discover the experiences in, and attitudes towards, marriage and sex relationships of English women, (2) to trace the association between certain childhood experiences and these relationships, and (3) to discover the factors associated with their feelings of happiness or unhappiness in marriage.

In order to achieve their results the authors compiled six different questionnaires, three for married and three for single women, and the major portion of the work consists of statistical analyses of the answers in the form of tables and graphs with associated commentary or amplification. There are innumerable cross references to matters which are considered to be of significant relevance. No fewer than 479 tables and 81 charts summarize the information and one quickly becomes lost in trying to extract some meaning from the welter of figures or draw some conclusion from the data given.

This work is essentially academic and one for the specialist in Sociology. The average doctor will find little practical use for the abundance of statistical information even if he has the time to plough through it.

One thing the work seems to confirm is the necessity for ensuring, in the interests of subsequent happy marriage, that children's early years are as happy and secure as possible. The figures emphasize that enlightened and sensible parenthood and intelligent sex education are essential to this end. As Dr. Chesser remarks in his summing up at the end of the book: "Only too often a vicious circle is created. A child may be starved of love because its parents are unhappily married, and no amount of legislation can give it the security for which it craves. If we look for the reason why the marriage is a failure, we may find it in the early childhood of both parents. Because they were deprived of love as children they are incapable of a satisfactory love-relationship as adults, and history repeats itself in their own child, and may be endlessly repeated in their descendants." If this book helps to prevent such perpetuation the writing of it will have been well worth while.

Diagnosis and Treatment of Peripheral Vascular Disorders. By David I. Abramson, M.D., F.A.C.P. (Pp. xv + 537; illustrated. £5 5s.) London: Cassell & Co. Ltd. New York: Paul B. Hoeber, Inc. 1956.

This book is written for "the busy family physician". It has three parts. The first, consisting of seven chapters, deals with "Differential diagnosis of symptoms and signs", and starts with the important subject of pain in the extremities. The various techniques used in studying the peripheral circulation, both arterial and venous, are then described in full. The section ends with a detailed account of the differential diagnosis of physical findings.

The second section is entitled "Peripheral vascular diseases" and forms the main bulk of the book. The final section gives an account of the relevant anatomy, physiology, pharmacology, and pathology. A useful appendix gives the nature of the proprietary drugs and instruments mentioned in the text.

The writing is clear and easy to read. This is a most useful book. The eighteen tables are particularly helpful; they are carefully constructed and are set out in such a way as to be very easy to use. The illustrations are mostly well-reproduced photographs. At the end of each chapter there is a list of references, many to papers written in English; however, it is surprising not to find Martorell's name mentioned. There is a marked medical bias, which is a good thing; surgical details would be out of place in a book of this type. The only important omissions are atrophie blanche and œdème bleu.

The weakest chapter is the one on "rare" vascular disorders. It is surprising to find erythema nodosum included under this heading. The section on stasis dermatitis is poor; no reference is made to the relation between the primary changes in that condition and in the other forms of capillarosis. There are a few minor inaccuracies such as the statement

that the non-tuberculous type of erythema induratum has been described in "recent years". Surely it is unwise to give treatment in bed precedence over ambulatory treatment for leg ulcers.

This is a beautifully produced book with a good index. The adverse criticisms are mostly of a minor nature. It is warmly recommended as a work of reference for practitioners and it will be of much use and interest to physicians and dermatologists. It is not intended for those who specialize in vascular diseases.

A Pictorial History of Medicine. By Otto L. Bettmann, Ph.D. (Pp. xiii + 318; illustrated. 72s.) Oxford: Blackwell Scientific Publications. Springfield, Ill.: Charles C. Thomas. 1956.

Of the making of medical history books and of medical historians who repeat one another, there is no end. Some histories consist almost entirely of names and dates and are useful only for reference; some are too erudite to appeal to the palate of the medical practitioner; others sacrifice accuracy to popularity. Dr. Bettmann's book is refreshingly different, being a snappy commentary on some 1,000 illustrations which tell their own story eloquently and graphically. The history behind this history is an interesting one, for it started with a cigar box. Toying with the idea of writing a pictorial history of civilization, Otto L. Bettmann, Ph.D., Curator of Rare Books at the Berlin State Art Library before the Second World War, began taking photographs of various details in famous paintings, such as food implements, costumes, operations, beards, spectacles, &c., &c. These were filed in a cigar box. With the help of books and documents he then compiled a card index listing his findings. In 1935 he transferred himself and his collections to New York City where he founded the *Bettmann Archive*—a unique collection which supplies historical prints on every conceivable subject to editors, writers, libraries, museums, business houses, and advertising agencies.

"A Pictorial History of Medicine", which starts with Egypt and the Ancient East and ends with Ehrlich, Behring, and Roux, is described as "a graphic record of the untiring efforts of the medical profession to cure the sick, offer solace, allay pain and secure a better life for all mankind". Essentially a non-technical survey, it is intended for the lay public who will find it absorbing and stimulating reading. But it can also be warmly recommended to the medical student, the practitioner, and the nurse who, no matter how pressed they may be for time, will enjoy the wealth of illustrations (many are rare, some are quaint, most are excellently reproduced, and a few are sadly disappointing), the economic, but breezy narrative, and the striking headings which whet the appetite. In a popular work the emphasis is necessarily different from that of a textbook, but on the whole the story of the healing art is well and accurately told. The author has read both widely and wisely, and he carries his learning lightly and unostentatiously. We are glad to find that, though there is a picture showing the Countess of Cinchon "receiving mythical dose of fever-bark tree", the accompanying text makes it quite clear that there is no foundation for this legend. Unfortunately, the drawing depicting Harvey at the battle of Edgehill, 1642, is not similarly "debunked". Proof-reading has been carefully done, though Halsted has an unnecessary "a" on page 301. "This is no 'pictorial souvenir' for the physician to inspect casually and then consign to the patients' waiting room", writes Dr. Philip S. Hench of the Mayo Clinic in his foreword. "Instead it should become a permanent member of his small, desk-side privy council." Dr. Bettmann concludes his book as the twentieth century begins, and we share Dr. Hench's hope "that this is not an end, but a pause, and that a companion volume will tell the fabulous story of medicine's last 50 years".

Symposium of Tuberculosis. Edited by F. R. G. Heaf, M.A., M.D., F.R.C.P. (Pp. xvi + 755; illustrated. 5 gns.) London: Cassell & Co. Ltd. 1957.

There have been a number of books on tuberculosis of recent years in addition to books on diseases of the chest which include tuberculosis, and it may be questioned whether this further addition to the literature is really necessary. Advances in this subject are so rapid that often by the time a book is published it may be out of date. Indeed, Professor Heaf in his introduction recognizes that "the time lag between the correction of the proofs and the final publication unavoidably means that reports are issued and new work is published, which unfortunately cannot be included in this work". Professor Heaf has, however, edited a comprehensive work on tuberculosis from every angle. He has rightly stressed the importance of the preventive aspects and other recognized experts have dealt comprehensively with the epidemiological, pathological, clinical, industrial and rehabilitation aspects as they affect the respiratory and non-respiratory tuberculous subject.

Moreover, childhood and adult tuberculosis is considered and the important aspect of "Tuberculosis in the Tropics" is not neglected. The book should have a wide appeal, especially in backward countries, where public health measures are less advanced.

A few minor criticisms can be made. A number of the illustrations are of poor quality and have not reproduced well. On the clinical side there are some who will question the amount of space allotted to collapse therapy, especially artificial pneumothorax in respiratory tuberculosis which, rightly or wrongly, with the introduction of antibiotic therapy is now very much on the decline. The high price of the book does not altogether seem justified.

Pulmonary Emphysema.—Edited by Alvan L. Barach, M.D., and Hylan A. Bickerman, M.D. 18 other contributors. (Pp. x + 545; illustrated. 80s.) Baltimore: Williams and Wilkins. London: Baillière, Tindall and Cox. 1956.

The subject of pulmonary emphysema is of great clinical significance and, in association with chronic bronchitis, is certainly responsible for much morbidity and mortality in Great Britain. The present volume, edited by Professor A. L. Barach and Dr. H. A. Bickerman of the Presbyterian Hospital, New York, contains contributions by men of international reputation who have done much original research in the field of applied physiology, pathology and therapeutics.

It is recognized that the functional pathology of the bronchi and lung parenchyma in emphysema can, with correct procedures to restore cardio-respiratory function, at times become reversible. These procedures, which must be used discriminately, include oxygen inhalation, antibiotic and steroid therapy, intermittent pressure breathing, chest remedial exercises, the use of broncho-dilator drugs (including aerosol therapy) and adequate bronchial drainage, &c. Continuous inhalation of oxygen is regarded as a valuable agent in the treatment of pulmonary emphysema, especially in the presence of acute hypoxia. The practical application, by many of the contributors, of their researches on respiratory physiology to the realm of therapeutics is noteworthy.

With multiple contributors a certain amount of overlapping appears inevitable and there are also some omissions. There is only one chapter dealing with the significance of infection —a considerable problem in this country. Although the pattern of diseases in the U.S.A. is probably different and chronic bronchitis is probably of less significance than here, one feels the subject might have been discussed more fully.

The book will, however, appeal to all physicians and particularly to those whose interests are directed to the important sphere of cardio-pulmonary disease.

Price's Textbook of the Practice of Medicine. Edited by Donald Hunter, M.D., F.R.C.P. 9th edit. (Pp. xiv + 1774. 63s.) Oxford University Press. London: Cumberlege. 1956.

Dr. Donald Hunter and his collaborators, and especially his publishers, are to be warmly congratulated on this new edition of "Price". A great deal of new material has been incorporated and the book is now indeed a "unique compilation of modern knowledge", eminently suitable to be put into the hands of those at the beginning of a career in any department of medicine in any part of the world. Valuable essays on normal function and on laboratory, radiological and other investigations introduce many of the descriptions of clinical entities. Some further exposition of the erythrocyte sedimentation rate, now so much used, and referred to here and there by various contributors, might profitably be added. It is a question, too, in a textbook of this calibre, whether more space should not be given to diseases of the eye. Glaucoma, for instance, is mentioned only as a complication of epidemic dropsy; and, in another section, it is surprising to find that carcinoma of the larynx is not mentioned at all.

The whole book is extremely readable, and the index is so good that the temptation to look for Tapanuli fever has to be firmly resisted!

A Companion in Surgical Studies. By Ian Aird, Ch.M., F.R.C.S. 2nd edit. (Pp. xii + 1302; illustrated. 84s.) Edinburgh and London: E. & S. Livingstone Ltd. 1957.

The outstanding reaction on reading the second edition of this work is admiration for the industry and scholarship of the author. The statement in the preface that there have been added "some thousands of references and nearly 2,000 of them to papers which have appeared since 1950" is an expression of this industry, which few if any potential authors of surgical textbooks in this country could emulate. Of interest, too, in this edition is the copying of the technique of textbook writing introduced in the United States a few years ago, whereby the

work is by a single author but with a consulting editorial committee behind him. The book is an excellent guide to surgical literature, particularly the more recent literature, but there is also frequent evidence of the historical scholarship of the author. The book apparently had its first origins in a collection of post-graduate lecture notes, presumably for final fellowship candidates. The acquisition of a large number of facts and opinions, and the ability to sift and balance them and come to a reasonable conclusion are still a part of the technique of success in the final fellowship, and it is probable that it is by fellowship candidates that this book will be most used. There is, however, a danger that an almost excessive balancing of literary references may train a candidate for something equivalent to a mediæval disputation, rather than educate him in surgery. This danger may perhaps be illustrated in the present work by the discussion of the almost mystical concept of "chronic mastitis". There is also a danger of arguments being put up only to be shot down. But the book must be judged not merely by the place it is likely to occupy in the affections of final fellowship candidates, but as an encyclopædic work of reference. The author's strong historical sense is demonstrated in the way he has tracked down the early references to many of the conditions he describes, e.g. the origins of blood transfusion; the pointing out that what is now generally known as Frey's syndrome was first described by Parkes Weber in 1898; and the reference to the first recorded case of spontaneous rupture of the œsophagus in 1724, occurring in a gluttonous Grand Admiral of the Dutch Fleet. One is surprised, however, that though Cutler's early work on mitral stenosis is mentioned, there is no reference to the much more important pioneer work of Souttar, from which the modern surgery of mitral stenosis in fact stems. It is obviously impossible to review a work of this character in detail, and any reviewer is bound to differ on some points from any author. But surely the statement that "in this country nodular goitre never seems to develop malignancy" is not true. Again, the standard treatment advocated for mixed parotid tumours is the theoretically admirable excision of the tumour together with its false capsule of compressed parotid tissue. But anyone with experience of parotid surgery knows that this is a quite impracticable procedure without routine preliminary identification of the facial nerve and its branches, when the operation becomes in fact the modern conservative parotidectomy. The recorded mortality for excision of the internal mammary chain in operations for carcinoma of the breast is nearer 0% than the "over 10%" of the author. And many surgeons would to-day reject the dogmatic advice that in the treatment of pilonidal sinus "skin and subcutaneous tissue must be excised *en bloc* down to bone over the whole area of suppuration", on the grounds of its being unnecessary and of the long delay in healing so often resulting from this procedure. But in spite of detailed criticisms such as these—which it would be unfair to stress except that they make one wonder how much the consulting editorial committee has in fact functioned—the abiding impression that this book has on the reader is one of amazed admiration for the author's industry and scholarship.

Outline of Fractures Including Joint Injuries. By John Crawford Adams, M.D.Lond., F.R.C.S. Eng. (Pp. vii + 248; illustrated. 27s. 6d.) Edinburgh and London: E. & S. Livingstone Ltd. 1957.

This is a simple, dogmatic, but reasoned account of fractures and their treatment, which can be accepted as representing the highest level of present-day practice. The work is designed for the medical student, the general practitioner and the physiotherapist, and starts from the premise that, since fractures are now treated for the most part in special clinics, the details of their treatment are for the specialist, as in the case of other surgical operations. The reader for whom this work is designed need only know the clinical evidence on which "he would suspect and recognize a fracture" and "the general principles of fracture treatment". This is a perfectly sound and legitimate philosophy with the provisos that it needs to be accepted also by examiners in final examinations, and that it is sound only under conditions such as obtain in this country at the present time. The main weakness in the acceptance of the philosophy in its entirety is the argument that, since medicine is in large part a practical art, the medical student who qualifies without himself being able to carry out such simple standard practical procedures as the efficient strapping of the chest for fractured rib, the reduction of a dislocated shoulder, or even the detailed management of a Colles' fracture, is not properly educated. The main question that arises is whether the author has lived up to his philosophy, and in general the answer is that he has, but with certain reservations. Thus, if it is general principles that matter, is the table of 30 causes of pathological fracture on page 14 necessary; or the drawings on pages 214 and 215 of the 14 different varieties of fracture around the ankle joint? The author has added to the interest of the book by brief historical footnotes on some of the chief names associated with fractures, but makes no mention of the key contribution of Böhler in the modern treatment of fracture. But these comments should not be allowed to obscure the fact that this is an excellent book.

Section of Radiology

President—Professor R. McWHIRTER, F.R.C.S.Ed., F.F.R., Hon. F.C.R.A., F.R.S.Ed.

[*January* 18, 1957]

DISCUSSION ON ANKYLOSING SPONDYLITIS

Mr. H. Jackson Burrows: Ankylosing spondylitis is a disease of unknown cause, of wide geographical distribution probably not identical with that of rheumatoid arthritis, and characteristically affects young men. It is a general disease with local manifestations, almost always first apparent radiologically in the sacro-iliac joints, and seeming to extend centrifugally to the lumbo-thoracic spine and costo-vertebral joints, the hips and sometimes the knees, and the neck and sometimes the shoulders; and seldom more peripherally. The very variable course tends towards arrest, which is possibly never complete. It is surprising that so distinctive a disease was not generally recognized sooner.

In a patient with the usual complaint of lumbar, gluteal or sometimes root pain and with a stiff back, sacro-iliac signs are rare, but three aids are useful:—a clinical sign: poor chest expansion; a radiological sign: sacro-iliac arthritis; and a pathological sign: raised erythrocyte sedimentation rate. Unfortunately, in the really early case these aids may be equivocal.

In radiological interpretation, the difficulty of distinguishing from other forms of arthritis, notably tuberculous, is well known. Two other particular difficulties arise. The more important is discrimination from the normal adolescent sacro-iliac joint, with its fluffy appearance but invariably intact joint space. The other source of difficulty is osteitis condensans ilii; but this always, or nearly always, affects women, the sclerosis is usually confined to the iliac side of the joint, and the joint space is preserved. In determining these points, oblique films in the planes of the sacro-iliac joints are invaluable.

The erythrocyte sedimentation rate, commonly but not invariably elevated, seldom settles—however seemingly quiescent the disease, which I think seldom, if ever, becomes quite extinct. The test, together with the patient's usual spareness and optimism, points to a general disease.

Less typical manifestations, well described by Golding (1936), are important because they may long precede the rest. Plantar fibrositis, with pain and tenderness at the posterior attachment of the plantar fascia, worse on rising, is sometimes the earliest indication, as in two young surgeons who first complained of painful heels in the operation theatre. Unexplained monarticular arthritis, in a young man's knee for instance, calls for radiography of the sacro-iliac joints. Similarly, iritis is sometimes a very early manifestation. Urethral discharge must be distinguished from that of gonorrhœa or of Reiter's syndrome. Differential diagnosis may require consideration of many spinal diseases: mechanical, degenerative, metabolic, infective and even neoplastic.

Deep X-ray treatment remains the chief standby. Cortisone and its kin are even more effective, but are ill-suited to a disease characterized by osteoporosis, often tuberculosis and often peptic ulceration. Their great use is for the frequent, complicating iritis. The value of exercises, especially breathing exercises, has long been recognized, but their exploitation has often been prevented by pain and spasm in the past before the advent of X-ray treatment brought these under control. Gravity-free exercises in pool or slings are particularly useful, and heat makes exercises easier and more effective. Adequate rest is a corollary of exercise, but does not imply fixation. Occasionally, still, a plaster bed at night is useful, but the patient must first be accustomed to it in hospital.

Although the patient should be encouraged to carry out all the activities within his remaining powers—and he seldom needs encouragement—it must be remembered that stiff joints and fragile bones predispose him to fractures, and that fracture of his spine will very likely cause paraplegia or tetraplegia.

Ankylosis of the lumbar and thoracic spine in good position implies little disability, but if the cervical spine or the hips are also fixed, the disability is great; if the knees also are fixed, the disability is very great indeed, especially if ankylosis is allowed to take place in the "anatomical" position, so that the patient cannot sit. Enthusiasm for the prevention of deformity is sometimes misdirected.

There is not a wide scope for surgery in ankylosing spondylitis. Mobilization of the ankylosed hip may be important. Formal arthroplasty is doomed to failure, but movement can often be obtained by excising the neck of the femur. The consequent instability of the hip can be diminished by a supplementary abduction osteotomy of the femur. The combined operation (resection-osteotomy) has been popularized by J. S. Batchelor. Whether accompanied by osteotomy or not, excision produces movement at the expense of stability, so that the patient has either to bend sideways to bring his centre of gravity over the hip at every step or use a stick; the patient with ankylosing spondylitis cannot bend his trunk sideways, and so is wholly and permanently dependent upon a stick after this operation.

Of osteotomies for ankylosis in bad position, osteotomy (or rather osteotomy-osteoclasis) of the spine is nowadays popular. It should be approached with great caution, because some patients have better function with than without their kyphosis, there is a real danger of paraplegia, and sometimes recurrence is inevitable.

I should like to conclude by acknowledging the great contributions made by radiologists to the understanding and treatment of this disease, and particularly my own indebtedness to Dr. F. Campbell Golding and Dr. Edward A. Allen of the Institute of Orthopædics and Royal National Orthopædic Hospital.

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Dr. J. W. Stewart:

The Effect on the Bone-marrow of the Treatment of Ankylosing Spondylitis with Deep X-rays

The development of leukæmia in patients with ankylosing spondylitis treated with deep X-rays (Court Brown and Abbatt, 1955) focused attention on the bone-marrow. This report is based on an investigation of bone-marrow from cases of ankylosing spondylitis undergoing radiotherapy in the Meyerstein Institute of Radiotherapy of the Middlesex Hospital.

There have been very few reports in the literature on the effects of deep X-rays on the bone marrow of living patients—occasional cases only having been reported by Nordenson (1935), Schulten (1937), Meller *et al.* (1938) and Leitner (1941). Denstad (1943), in an excellent paper, surveyed the previous work and reported many detailed results of his own investigations into the subject. Included among his cases are four patients suffering from ankylosing spondylitis. Hutaff and Belding (1955) reported the results of marrow examinations from ilium and sternum in 10 patients with carcinoma of the cervix undergoing treatment with deep X-rays and radium.

METHODS

Bone marrow specimens were obtained by the following methods: (1) Puncture with a Salah needle. This method was confined to the sternal marrow. The site chosen was usually the manubrium but in a few cases the first or second piece of the sternal body.

(2) A small trephine using a Turkel and Bethell needle. The instrument used was manufactured by Messrs. Down Bros., and the large size was always used. This gives a small piece of bone about $\frac{1}{8}$ in. in diameter and about $\frac{1}{4}$ in. long. After removal of the trephine a syringe and adapter were attached and 0·25 to 0·50 c.c. of marrow was aspirated, as when a Salah needle was used. Smears were invariably made at the bedside directly from material in the syringe. 300–500 cells were counted on each smear. The remaining aspirate was placed in an oxalate tube for total cell count. This instrument was used on the manubrium sterni in a few patients and in all patients in whom iliac marrow was examined. The site chosen was just lateral to the posterior superior iliac spine. This is a readily accessible

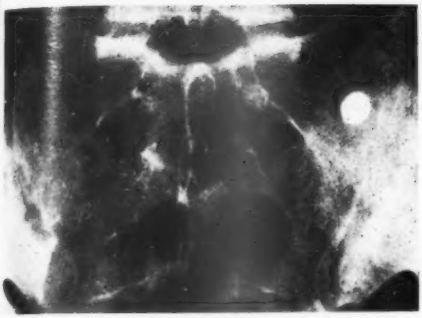


FIG. 1.—Area irradiated in treatment of sacro-iliac joints. Marker shows site of examination of iliac marrow.

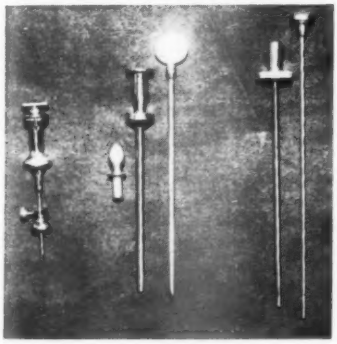


FIG. 2.—Needles used for obtaining the bone-marrow specimens. The small needle on the left is the Salah needle used for the sternal marrow specimens. The remaining instruments are the parts of the Turkel and Bethell needle.

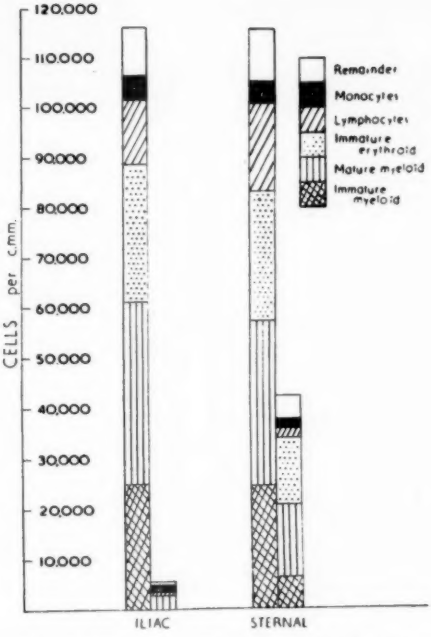


FIG. 3.—Histogram illustrating the effect of deep X-ray therapy on sternal and iliac bone marrows from Case I. In each case the left-hand column represents the result of examination before treatment.

portion of the ilium, the muscle covering being thin and the bone thick, and satisfactory specimens easily obtained. This site is also well inside the treatment area in those cases in which the sacro-iliac joints were irradiated (Fig. 1).

Fig. 2 is a photograph of the instruments used.

MATERIAL

Observations were made on 76 patients attending the Meyerstein Institute of Radiotherapy. Treatment was given with X-rays generated at 200–250 kV. of quality represented by a half-value layer of 0·8–1·3 mm. Cu, at a focal skin distance of 40 cm. A skin dose of 2,100 r–1,900 r was normally attained in fields directed to the spine and sacro-iliac joints. In one patient, iliac and sternal marrow specimens were taken simultaneously with the Turkel and Bethell needle before treatment and seven days after it had finished. This is a representative case and I propose to examine the result in detail.

Fig. 3 is a histogram showing the results of the iliac and sternal marrow examinations from this patient. The left-hand column of each pair is the pre-treatment specimen. There is no significant difference between iliac and sternal marrow before treatment. In each case cellularity is higher than normal but otherwise the marrow is within normal limits.

Seven days after treatment the iliac marrow specimen indicates complete aplasia. The cellularity is very low and no immature erythrocyte or granulocyte remains of the marrow cells, only polymorphs, lymphocytes, monocytes and reticulum cell remain although in greatly reduced numbers. The number of monocytes and reticulum cells are least reduced and so there is a relative preponderance of these types in the marrow count.

The sternal marrow specimen also taken seven days after the end of treatment shows

reduction in cellularity to a normal level. All types of mature and immature bone marrow cells are present but there is some reduction in the number of immature myeloid cells. The immature erythroid cells are relatively less affected and now constitute 31% of the cells present whereas the normal proportion is less than 25%.

Fig. 4 shows the results of iliac marrow examinations before and after treatment in some

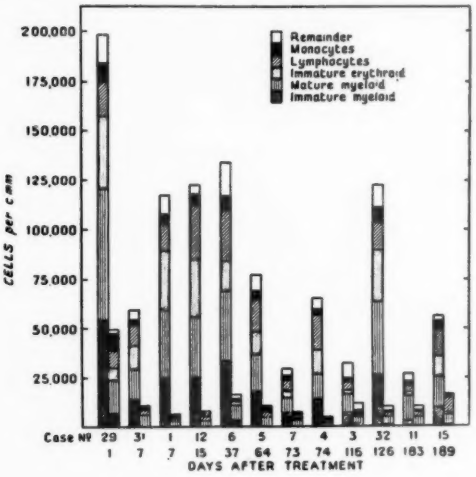


FIG. 4.—Effect of deep X-ray therapy on bone marrow included in treatment area. In each case the left-hand column represents the result of examination before treatment. [(1956), *Lancet*, ii, 1063. By kind permission.]

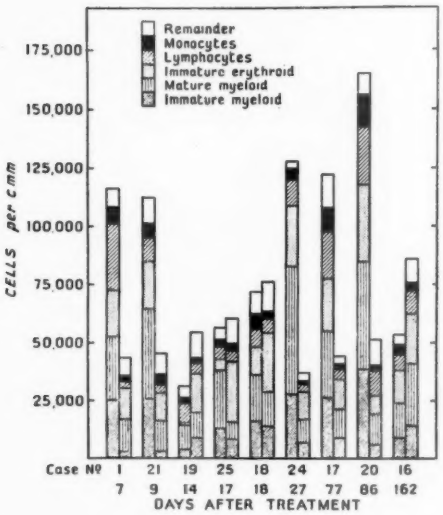


FIG. 5.—Effect of deep X-ray therapy on bone-marrow distant from treatment area. In each case the left-hand column represents the result of examination before treatment. [(1956), *Lancet*, ii, 1063. By kind permission.]

other cases undergoing deep X-ray therapy. Again, the left-hand column of each pair represents the pre-treatment specimen. The post-treatment sample has been taken at intervals of between one day and six months after the finishing of treatment. It can be seen that from about one week after the end of treatment until at least two months later the bone-marrows are aplastic and no immature myeloid or erythroid cells are present. After this time a very few immature cells make their appearance but even six months later the marrows show a very severe hypoplasia.

Fig. 5 is a histogram of the results of sternal marrow examinations in patients being treated with X-rays for ankylosing spondylitis. This site was chosen as it is convenient and at the

same time not directly within a treatment area. The left-hand column of each pair represents the pre-treatment specimen and once again punctures are done at varying intervals in each case from one to twenty-three weeks after the end of treatment. The response of the marrow distant to the site of treatment appears to fall into two types. In the first category represented by these patients who had hypercellular marrows before treatment (Cases 1, 21, 24, 17 and 20 in Fig. 5) the immediate result was a reduction in cellularity to normal levels. In each case the reduction was most marked in the case of the immature myeloid cells, although absolute numbers of all cell types were reduced. In the second category, represented by these patients in whom the marrow cellularity was within normal limits at the commencement of X-ray therapy (Cases 19, 25, 18 and 16 in Fig. 5) there was little alteration in cellularity after treatment, but there was a change in the myeloid/erythroid ratio especially during the first six to eight weeks following the cessation of treatment by X-rays. These cases all showed an erythroid hyperplasia associated with a mild degree of myeloid hypoplasia.

Denstad (1943) and Hutaff and Belding (1955) observed a similar erythroid hyperplasia in marrow distant to site of treatment. This finding is difficult to interpret. The most obvious explanation is that hyperplasia is compensatory as the iliac bone-marrow is aplastic at this period. But this cannot be the full explanation as the iliac marrow is still aplastic after the sternal marrow has returned to normal limits. It may be that hyperplasia is temporary compensation until a redistribution of hæmopoietic activity has occurred and that normal inactive marrow, e.g. in the femoral shafts, has resumed hæmopoietic activity to replace marrow rendered aplastic in ilium and spine by the deep X-ray therapy. This has not yet been proved but might gain some support from the results of the peripheral blood counts, since all cases of ankylosing spondylitis under treatment show no significant alteration in hæmoglobin concentration but a marked leucopenia, particularly neutropenia, which has largely recovered by the end of the second month after therapy has ceased.

The use of the Turkel and Bethell needle enables a small bone and bone-marrow biopsy to be taken and a section of such a specimen is shown in Fig. 6. This is from the iliac bone

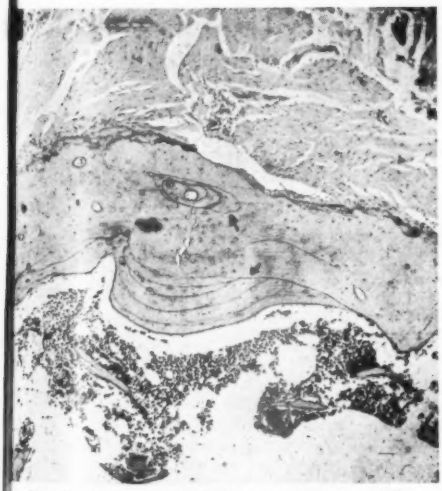


FIG. 6.—Iliac marrow before treatment. ×75.



FIG. 7.—Iliac marrow from Case 1 after treatment. ×75.

of Case 1 discussed previously. The periosteum and bone are normal and there are cement lines (arrowed in Fig. 6) indicating that bone has been recently laid down. The marrow is more cellular than normal but is otherwise unremarkable. Fig. 7 shows a similar specimen removed from the opposite ilium seven days after deep X-ray therapy has ceased. The periosteum is somewhat acellular and the bone looks normal and lacunæ contain bone cells. But cement lines are completely absent. This has been noted in many post-treatment specimens in these patients. The bone-marrow is aplastic—only a few polymorphs, monocytes, lymphocytes, reticulum cells, occasional plasma cells and fatty tissue remain.

This is an invariable finding in these patients receiving 2,000 r or over. Fig. 8 and are high-power views of the pre-treatment and post-treatment marrow specimens respect ely.

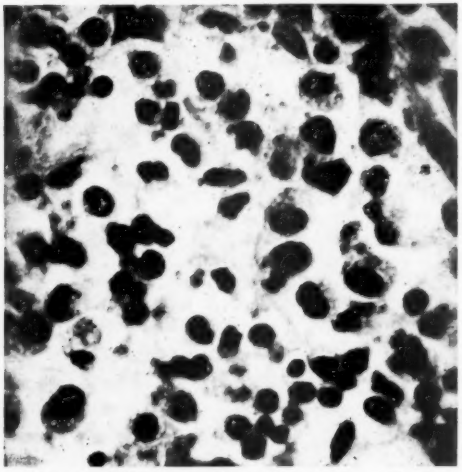


FIG. 8.—High power view of iliac marrow from Case 1 before treatment. ×565.

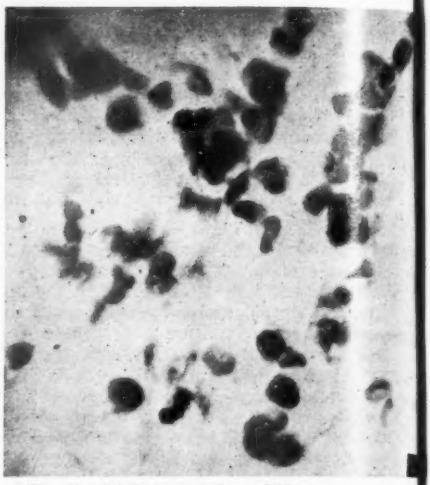


FIG. 9.—High power view of iliac marrow from Case 1 after treatment. ×565.

A special search was made into the bone-marrow smears for abnormal cells. Before treatment osteoblasts were present in large numbers in a sternal marrow smear from a patient who had no symptoms referable to the sternum. This is a most unusual finding especially in adult marrow specimens. Osteoclasts were occasionally seen. In post-treatment marrow specimens from a treatment area giant polymorphs were occasionally seen. Monocytes with vacuolated cytoplasm and nuclei were a very common finding. These are not specific or unique to deep X-ray treatment but they are encountered much more frequently in the marrows of patients who have such therapy. Mitotic figures are virtually non-existent, but as the time after the cessation of the deep X-ray therapy increases, they can be found in slowly increasing numbers.

I wish to thank Professor B. W. Windeyer and Miss M. D. Snelling for allowing me access to their cases and to Dr. S. Dische for his help and co-operation.

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Section of Laryngology

President—J. ANGELL JAMES, M.D., M.R.C.P., F.R.C.S.

[*February* 1, 1957]

DISCUSSION ON FACIAL AND PALATAL REPAIR IN THE TREATMENT OF MALIGNANT DISEASE

Mr. W. A. Mill: Malignant disease of various types may affect the different tissues and structures making up the face and mouth. In the majority of cases treatment in the first place is by radiotherapy. Sometimes no further treatment is needed but only too often surgical excision has to be undertaken. Not surprisingly in a number of cases gross deformity results. This is an outline of the corrective procedures that are undertaken to restore function and comfort to the patient. It is desirable that the patient should continue to live as normal a life as is possible and that he should not be afraid of meeting his fellows. His appearance therefore must be made as good as it reasonably can be. Repair may be necessary following treatment of growths involving the upper or lower jaws, the cheek, the lips, and the palate; growths of the nose may extend to the cheek and to the orbit and ethmoid or even the upper jaw and this is notoriously so of basal cell carcinomata.

Many of the patients are old and they have had treatment of various kinds extending over many years and quite often there have, in the past, been a number of operations to deal with repeated recurrences. In many cases previous radiotherapy has made the tissues rather devitalized so that healing may be difficult if a further operation is undertaken. Many patients, particularly the old, are most unwilling to have further operations. In deciding what repair is to be done it is necessary to keep these points in mind.

Excision, if it is undertaken, must be adequate. Before operation multiple biopsies will have shown the extent of the malignant disease and at the time of operation use should be made of the frozen section technique to ensure that removal of the growth is complete. With basal cell carcinomata some recurrences are certainly true recurrences but in some cases one seems to be dealing with multiple new foci. Although involvement of lymph glands is exceptional with rodent ulcers the neoplastic cells may invade the skin lymphatics and secondary nodules may be seen near the main lesion.

Immediate repair.—A certain amount may be done at the time of operation to minimize deformity and to accelerate healing. Where it is possible Thiersch grafts should be applied so that rapid epithelialization and the prevention of scar tissue formation may result. When it can be done the sewing of mucosa to the skin has a similar effect. This is important to keep the tissues in as good condition as possible with the minimum of scarring, especially if subsequent plastic operations are to be undertaken.

In some cases partial or complete repair can be done by transposed skin flaps, particularly about the ear.

Of course a good window must be left to make sure that any recurrence will be noticed and for this reason the covering of cavities should not, as a rule, be done at the time of the operation of excision.

Palate.—If it is intended to remove part of the hard palate, a prosthesis should be made before operation so that it can be worn after operation, perhaps the following day, or a day or two later. This adds to the comfort of the patient. Later, of course, when healing has occurred a permanent obturator is made. These are as a rule satisfactory even in the edentulous but if there are teeth in the opposite maxilla fixation is of course easier to obtain. Occasionally the palate may be repaired by plastic surgery by sewing the margin of a re-formed cheek on to the palatal edge.

Later repair.—It must be emphasized that it is usually wise to wait for a long period before undertaking any major plastic reconstruction. It is essential to ensure the absence of the recurrence of disease and as a rule only the passage of time will give this certainty. During the period before operation a temporary prosthesis is a great help and comfort.

In the young, if it is at all possible, plastic procedures should be carried out. In the old however, the correction, or perhaps one should say covering, of the deformity can well be done by fitting a prosthesis. This is usually of acrylic resin but sometimes it is made of metal. The prosthetic appliance is tinted to match the patient's colouring and usually very good results are achieved. The colours of the prosthesis do fade in time and the appliance gets dirty and so renovation is necessary at intervals.

Growths of the antrum and palate.—In many cases a very long sublabial incision passing well to the healthy side is all that is required in removal of the palate or partial removal of the upper jaw. The whole maxilla can easily be removed through such an incision. The only repair needed is an obturator to close the opening in the palate.

It is sometimes necessary to make an incision in the face by the side of the nose with division of the upper lip and this will give a better exposure. At times extension of the incision laterally through the lower conjunctiva may be required and this incision may be prolonged outwards from the external canthus in some cases. These incisions heal with little scarring. Any incision across the side of the face below the eye is likely to result in persistent œdema of the lower eyelid.

Sometimes the skin of the cheek is invaded by growth and must be excised. A gap in the cheek may have to be left. Where possible mucosa and skin should be sewn together or possibly Thiersch grafts applied. If the gap is not too large it may be closed by suturing at the time of the operation. If a gap remains later plastic operation may be necessary. In some patients, however, a prosthetic appliance answers very well. On the whole in younger patients it is best to try to obtain a covering of natural tissues by plastic operation.

Sometimes after operation on the upper jaw there is scarring with raising of the corner of the mouth which may be corrected by a relatively minor plastic operation (epithelial inlay). At other times subsequent necrosis of bone, particularly of the malar bone, may produce unpleasant deformity which a plastic operation could correct.

Usually the eye does not drop even if the orbital floor, that is the antral roof, is removed, but it may do so if the removal of bone has to be carried high on the inner and outer sides of the orbit. However in my experience the resulting diplopia is not as a rule persistent. No dental obturator will hold up such a fallen eye.

After removal of the maxilla mucosa readily covers the raw area. Some surgeons skin-graft the walls of the cavity but this does not seem to be necessary.

Nose.—When the nose has to be removed repair may be by plastic operation or by prosthesis. In the young there is a strong place for plastic reconstruction but in the older patient a plastic nose is very satisfactory.

Orbit and ethmoid.—If the orbit has to be exenterated the skin of the eyelids should, if possible, be preserved to give a partial lining to the cavity and the rest may be covered by Thiersch grafts. If the orbit alone has been exenterated or the orbit and ethmoid, many patients prefer to wear an eye patch—an eye patch is so often worn that the appearance is not unusual. A plastic prosthesis with an artificial eye looks well in photographs but the eye does not move and looks unnatural. Many patients prefer a plain skin-tinted prosthesis worn with a patch or an opaque spectacle lens. It is certainly not advisable to cover the orbital opening with a skin flap—it is still unsightly and has to be hidden from view in some way.



FIG. 1 (1950).—Epithelioma of nose and eyelid following lupus.



FIG. 2 (1951).—Result of excision. (W. A. M.)



FIG. 3 (1956).—Patient wearing prosthesis.

Cheek and lower alveolus.—Growths involving the lower jaw are largely outside the scope of this discussion. The problem of repair may well involve a temporary prosthesis for some time and subsequently plastic procedures and even bone grafting. The same considerations apply to growths of the cheek which often involve the lower jaw and sometimes the upper jaw.

Ear.—The ear is a most difficult structure to build adequately by plastic surgery. The prosthetic ear is most satisfactory and it is the general method of repair used. At the time of operation a good deal of immediate repair may be done by Thiersch grafting and the arranging of transposed flaps. It is important to graft the external auditory meatus at its entrance, to avoid stenosis.

It will be seen that the aim is to obtain good function for the patient and at the same time a reasonable appearance. It is important in the old, who have suffered a great deal in the past, to remember that too many operations have spoilt their lives. Much may be done to help them with prosthetic appliances.

I wish to thank Mr. R. J. V. Battle for his co-operation in the treatment of many of the cases and also Mr. J. H. Hovell, who has undertaken the making of palatal prostheses. I must also thank Mr. F. R. Coffin of the Royal Marsden Hospital, who has made the palatal prostheses for many of my patients.

Mr. R. J. V. Battle: In facial reconstruction for malignant disease many factors must be considered.

Firstly: There is one golden precept that must always be followed: Once the diagnosis of malignant disease is made there must be no delay in the eradication of this disease by any preliminary preparation of complicated reconstructions. For example there should be no preparation of flaps that might delay treatment.

Secondly: Pathological considerations only should be allowed to dictate treatment. Fortunately the greater number of lesions reaching the surgeon are purely surface lesions and of these the majority are rodent ulcers.

SURFACE LESIONS

(1) *Rodent ulcers.*—Nearly all of these, except those round the eye, have been irradiated and have recurred. Some have been considered too wide and penetrating for irradiation. One group of deeply infiltrating lesions require extensive surgery if they are not to recur locally. Moreover they produce by some trigger action, not fully understood, other primary lesions in the neighbourhood, so that the extent of the primary excision is no guarantee against recurrence.

Very fortunately none of these lesions metastasizes, but in the infiltrating group early reconstruction is contra-indicated, and wherever possible a prosthesis must be considered for the interval during which recurrence might be expected.

(2) *Squamous cell carcinomata.*—These are very much more rare in white skins than are the basal cell lesions. The reaction of these tumours round the lips to irradiation has perhaps explained why reconstruction of the upper and lower lips is so much less in demand than would appear to have been the case in the last century. The devastating spread to glands and occasional dissemination in the blood stream make one feel that early complicated reconstructions are a waste of time, and that the fitting of a prosthesis for a period of at least two years is a more sensible procedure.

(3) *Malignant melanomas.*—With the appalling prognosis extensive reconstruction is out of the question, but may be indicated on two grounds. Firstly where function is grossly disturbed—e.g. with a large defect into the oral cavity—or secondly where there is great disturbance of morale, and it is imperative that the patient should be reassured or rather "kidded" into thinking that the removal of the local lesion means the end of all anxiety.

(4) The rapidly-growing anaplastic tumours may react to irradiation and very few need be considered for serious reconstructive surgery.

DEEP LESIONS

From the point of view of reconstruction these fall into two groups:

(1) Those affecting the antra, the nose and the palate—i.e. the middle third of the face. These can again be subdivided into two groups:

(a) When skin covering is not affected.

(b) When the skin covering must be removed.

Group A.—The chief reconstructive problem falls to the lot of our dental colleague and

is limited to obtaining rapid healing (perhaps with the help of an epithelial inlay), the camouflage of the falling in cheek by the same method, and the restoration of function by the provision of a denture. Where necessary the reconstruction of the palate may be effected by the introduction of skin. This must be transferred from a distance as a tubed pedicle flap by a fairly lengthy and difficult process, and only when the fear of recurrence is minimal and the procedures can be carried out at leisure.

Group B.—The early provision of a skin covering is a debatable problem. There must be a real danger of masking a recurrence by such an early procedure. I have, in my own small experience, seen several patients in whom recurrences deep in the nose have been missed and the patient eventually lost by too early reconstruction. The exact time factor in this problem is difficult to determine. It is possible that an examination of the tissue removed will give the clue. I used to work on a standard time lapse of one year between excision and reconstruction but I doubt if this is long enough. I think that two years may be the better interval of time—the patient getting on with a prosthesis during that period.

(2) Those lesions affecting the tongue, lower jaw and glands of the neck. Briefly, the problem here is that of removing the tumour with its entire lymphatic field as a single tissue mass at one operation. In the more advanced cases very great ingenuity is required in order to obtain a watertight closure of the buccal cavity, and in obtaining an ample supply of viable skin covering from the neck. In these patients no external prosthesis can ever replace the watertight closure of normal tissues, and for practical purposes need never be considered, unless it be in the form of a simple cup in which dressings are contained.

Thirdly: Anatomical considerations.

THE EYE AND THE EAR

The eye and the ear present special problems of their own.

(1) *The eye.*—Destruction of part of one or of both eyelids must at once be followed by reconstruction, or else the eye is lost. With any invasion of the orbit, this has to be exenterated leaving a large raw surface of bone to be covered. It has usually been my practice to employ the forehead for this cover—a somewhat extravagant procedure that has two advantages. Firstly it is an insurance of quick healing with a durable skin cover that will bear the weight of a prosthesis, and secondly this will also stand up if necessary to irradiation of any subsequent recurrences. Against the immediate use of the forehead the orbital bone readily accepts a Thiersch graft and the forehead can be spared for use later, should recurrences lead to a necessity for exposure of the cribriform plate or the dura or the underlying brain itself.

Furthermore no reconstruction can produce anything similar to the normal eye with its movements, and eyelids with their closure, and there is therefore only one ultimate fate for these patients who have had an exenteration—a prosthesis to conceal their deformity from the prying eyes of their fellows. A ground glass in their spectacle frame is not enough. The prosthesis can be a simple eye shade in type that conveys the Nelson touch, or else it can be more complicated and can carry an eye and an eyebrow.

(2) *The ear.*—There is not the same urgency in dealing with the ear that there is with the eye. Small losses may be made good at leisure. Removal of the ear in an adult must be followed by the wearing of a prosthesis. The only indication for total reconstruction of the ear in an adult must be an inability on the part of the patient to tolerate the gadget. If he demands a reconstruction then it must be pointed out that many stages will be necessary and that the final object will in no way resemble an ear!

In the severe cases in which the lateral sinus and dura become exposed, and certainly in those where the temporo-mandibular joint remains open to the four winds, a scalp flap is always available to produce the necessary protection and backing for the subsequent prosthesis.

In all severe lesions involving the eye and the ear our only problem is to obtain early healing with sound skin cover and then to organize a camouflage by artificial means.

Fourthly: Other factors which influence our treatment. These patients are mostly in the older age groups, few are under 50 years of age and many are over 75. Many of them, often out of sheer perversity and in anticipation of the horrors of a surgical operation, have held on to their lesions for long periods of time. These are poor material for reconstruction with its repeated surgery, discomfort and hospitalization. It follows that we often adopt the prosthesis where against a more normal psychological and physical background we would prefer flesh and blood.

Another factor is the effect of irradiation. The presence of a new growth in a field that has been heavily irradiated means at once a multiplication of all the hazards attendant on the transfer of skin flaps, the take of skin grafts and on even the simplest forms of wound suture.

We have come, therefore, to consider reconstruction in this field under two headings:

(1) *The immediate repair.*

(2) *The delayed or "interval" reconstruction.*

(1) *The immediate repair.*—In the immediate repair we are not only concerned with the raw surface left by the wide excision of the lesion—we have to prepare the stage for any subsequent procedures.

If the lesion is superficial and if the pathology is not fully understood, then the immediate application of a free graft is advised. In the smaller lesions the post-auricular Wolfe grafts have become increasingly popular on account of the improved cosmetic result obtained.

A flap is required for the immediate repair under the following conditions:

(i) Deficiencies in the eyelid of full thickness.

(ii) Where cortical bone is exposed (the only exception being the orbit which will take a free graft).

(iii) Where the dura, lateral sinus or temporo-mandibular joint is exposed.

Wherever possible the employment of a local tissue flap should be considered—either as a transposition or as a rotation. If not available then a forehead flap must be brought down.

In large defects in the upper face—e.g. into the buccal cavity, or after amputation of the nose—careful suture must be planned of the marginal skin to the mucous membrane of the lining of the cavity. This is not merely to obtain rapid healing *per primam*, but also to minimize the degree of marginal scarring. We are, in fact, preparing for the later reconstructive phase when it may well prove desirable to turn lining flaps based on this very margin.

Many of the lesions that we see are recurrent lesions where there has been an extensive irradiation of tissues. The failure to appreciate the extent of tissue damage and the inability to replace all such devitalized tissue by reason of its sheer extent are potent reasons for defeat. This applies particularly in the employment of local flaps and in the repair of lesions of the lower third of the face, where a watertight closure is essential in the primary repair.

(2) *Delayed or "interval" reconstruction.*—In the ear and after exenteration of the orbit the employment of a prosthesis can be described as satisfactory only in that it allows the victim to wander unnoticed amongst his fellows. It must, however, be very irritating and depressing to have to "dress up" every time you leave the house, and there is the constant fear that you may lose a vital part of your "make up" every time you run for a bus or look out of a carriage window. Here indeed surgery has proved wanting and further progress must be looked for.

In the nose, however, the cosmetic prosthesis is far less satisfactory—not that it is inferior to most of the noses reconstructed in flesh and blood. The simple fact is that you can blow a reconstructed nose and that you cannot blow an artificial one. Surgeons of many generations have studied this problem. The earliest technique employed is the Indian method, by which the forehead is brought down. This technique gives the best nose, but produces a secondary defect that in the male is better avoided if possible. Then the Italian method, by which the upper arm is employed to provide the flap, gives nice results but entails maintaining the arm in a somewhat fixed position. In the older patients I should say that this method is contra-indicated.

A tubed pedicle raised on the chest is a little difficult to handle but entails a less fixed position and can be brought up to the nose without the use of a vehicle to transport it. The male chest may be too hairy, and in the female any scar on the chest is better avoided except in older patients.

Such a pedicle can be transported from the abdomen on the wrist and brought up to the face. Again in this technique we are up against an agonizing period of immobilization of the arm. The colour match tends to be disappointing.

In all I favour the forehead in most cases but would only adopt any particular method after a full discussion with the patient.

Large defects in the middle third of the face or of the buccal cavity must be closed by the introduction of one or more flaps: all the flaps mentioned—forehead, arm, chest and abdomen—being available. Furthermore the flap introduced for cover must either carry its own lining or else lining flaps must be planned and brought into position simultaneously. It is in the provision of this lining that the greatest ingenuity is required and the various techniques involved can be summarized as follows:

(i) Flap for covering, lined with Thiersch graft. Such a lining is not advised if bone will later be introduced either for contour restoration or to replace missing mandible.

(ii) Local flaps turned over to act as lining—not possible if the area has been heavily irradiated. In all cases they are better not delayed, since they are raised and turned through an angle of 180 degrees and based on scar tissue. These flaps are very vulnerable.



FIG. 1.



FIG. 2.

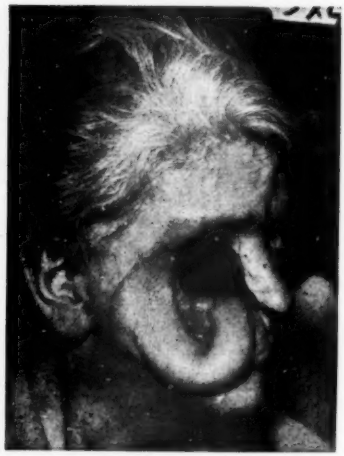


FIG. 3.

FIG. 1 (September 1948).—Extensive rodent ulcer under treatment by H.V.T., by Professor D. W. Smithers.

FIG. 2 (March 1950).—After excision and Thiersch grafting. (Operation by W. A. M.)

FIG. 3.—To show method of repair (R. J. V. B.).

(iii) The introduction of one flap (e.g. forehead) for covering another flap (e.g. chest) for lining.

(iv) The insertion of a flap all round the margin of the defect. When this has settled in, a part of it is turned in for lining and the rest spread across for covering.

Finally there are a series of operations by which we can assist the dental prosthetist and in this way improve function:

(*a*) Epithelial inlays.

(*b*) The introduction of tubed pedicle skin to repair the palate.

(*c*) Freeing jaw fragments in order to obtain a better occlusion.

(*d*) The repair of the upper lip—with special emphasis on the Estlander and the Abbé procedures.

(*e*) Finally the closure of the mouth from the rest of the face in those extensive lesions in which the greater part of the face has been removed.



FIG. 4 (February 1953).—Condition after plastic repair by R. J. V. B., showing re-formed palate and lower cheek.



FIG. 5 (June 1956).—Wearing prosthesis.

CONCLUSIONS

(1) The pathology of the lesion dictates the reconstructive programme. The possibility of a recurrence being masked by the repair swings the balance towards the use of a temporary prosthesis until the chance of recurrence is minimal.

(2) Severe lesions of the ear and eye are best treated by a prosthesis. Reconstruction has little to offer here as yet.

(3) The age and attitude of the patient will dictate the ultimate degree to which reconstruction will be possible, and may lead to the selection of a prosthesis where normally flesh and blood might have been preferred.

(4) A brief résumé of the procedures available both in immediate and delayed reconstruction is given with examples, the emphasis being on the restoration of function rather than of appearance.

Mr. J. H. Hovell: The dental surgeon is gravely handicapped both in the immediate post-operative period and in the long-term prosthetic management of these cases if he has not had the opportunity of seeing them pre-operatively.

The ideal is personal consultation between surgeon and dental surgeon as soon as operation has been decided upon. The probable extent of the excision, the number of teeth which can be left and the need for post-operative radiotherapy are all of importance if the best possible results are to be achieved.

The next step is to obtain duplicate pre-operative models of the patient's jaws, and, should he be edentulous, also one of dentures. One of these and that of the dentures is kept as a permanent record, the other is used for the construction of the immediate post-operative appliance.

It has been found desirable that an appliance should be constructed before operation for immediate post-operative insertion. This appliance (Fig. 1) performs several functions:

(1) It maintains the pack in position, prevents it from being disturbed by the tongue and minimizes contamination by food.

(2) It is a great aid to speech and deglutition.

This prosthesis which is made in duplicate is constructed to conform to the original shape of the patient's palate and alveolar process. If teeth are present on the unoperated side these are used for retention and a flat biting surface is provided on the other side of the same vertical height as the original teeth.

When the patient's own dentures are available it is unnecessary to construct a duplicate appliance as the former will act perfectly as the first prosthesis and to maintain the pack. A second upper denture is, however, made before operation to act as a base later for the second prosthesis.

The most comfortable pack for use after the removal of the initial post-operative packs has proved to be a small marine sponge, cut, if necessary, to the approximate size and shape of the cavity.

The length of time during which this appliance continues to give service depends greatly upon whether or not post-operative radiotherapy is employed.

Post-operative radiotherapy is a major difficulty for the dental surgeon as it gives rise to a slowly healing cavity which continues to change shape and to sequestrate bits of bone, often for as long as twelve months. During this period frequent adjustments have to be made to the prosthesis in order to maintain the patient in reasonable comfort.

Normally speaking it is a good rule that prior to radiotherapy about the mouth all teeth should be removed, in order to minimize the risk of osteo-radio-necrosis arising subsequent to a later extraction. This danger of radio-necrosis is such that some authorities—Kelsey Fry for example—consider even the wearing of dentures to be dangerous.

This rule, however, is not adhered to when dealing with radiotherapy following surgical extirpation of maxillary neoplasms for the following reasons:

(1) Radio-necrosis is far less likely to occur in the maxilla than in the mandible.

(2) The radiation is localized within the cavity and not "beamed" through the teeth, thereby minimizing remote effects and "scatter" from the teeth.

(3) The retention of teeth is extremely desirable. First they are the greatest possible aid to the retention of a prosthesis. Second they may be needed to support an appliance carrying a tray for an epithelial inlay in a subsequent plastic repair.

(4) They seldom have to be extracted as the strain of helping to support a prosthesis ultimately invariably causes them to be loosened and finally to drop out from a socket lined with granulation tissue from which the bone has completely receded. It has not yet been my experience to see a radio-necrosis arising in the maxilla as a result of a tooth being lost in this way.

It is, of course, necessary to remove the teeth immediately adjacent to the area excised, and the remaining teeth should be carefully watched and conserved so as to eliminate the possibility of abscess formation following carious exposure of the pulp.

Until healing of the cavity is fairly complete and all major sloughs and sequestra have separated, it is undesirable to attempt to obtain an exact impression of the whole cavity. The suction created and the difficulty of removing an exact impression may at this stage give rise to a severe secondary hæmorrhage.

If, therefore, a method of radiotherapy necessitating an exact cavity impression is to be employed, this must be taken at the time of operation before the cavity is packed. This is not done at St. Thomas's where the radiotherapists prefer to irradiate the cavity with one large needle placed centrally in a marine sponge.

The degree of comfort obtained with this first prosthesis and a sponge is such that there is no urgency to replace it with a more accurately fitting appliance and I usually wait for three to four weeks when the cavity is fairly clean and the surgeon gives the "all clear" for the next stage.

The most important factor for the comfort of the patient wearing a prosthesis is the maintenance of a complete peripheral seal to the cavity. Even at this time it is impossible to obtain a total impression but by building up the prosthesis already constructed with soft wax a rough outline of the cavity margins is obtained. An accurate impression of these is then taken with elastic impression material using the prosthesis as a base.

Having obtained the impression the next problem is to obtain maximum retention and stability. Neither at this time nor later when healing is complete can undercuts in the cavity be used as an aid to retention. The inevitable movement that occurs causes rubbing and ulceration of the mucosa if this is attempted. With this prosthesis, therefore, stability must depend upon the elimination or reduction to a minimum of any possible displacing factors.

The first and most important of these is the weight of the appliance. Because of this it is made as light as possible, and no attempt is made to construct a bung going up into the cavity. The second displacing factor is the movement of the teeth and occlusal forces during mastication. To eliminate this the biting surfaces of the teeth are set up on an anatomical articulator designed so that the movements of the jaw are exactly duplicated. In this way cuspal locking is avoided and the bite balanced in all excursions of the mandible.

The third displacing factor is the soft tissues. Normal activity of the oro-facial muscles exerts forces upon the prosthesis. These forces are balanced before removal of teeth between the tongue inside and the muscles of the cheeks outside. This then is the reason for obtaining records of the patient's own teeth or dentures before operation. The dental arch of the prosthesis must be the same as that present before operation in order that this balance of forces should not be disturbed.

In addition to activity there is also the effect upon soft tissue morphology of the surgery. Scarring and contraction of the tissues is frequent with resulting changes in facial contour. It is useless to attempt to correct these changes by the prosthesis, as the tissues will not permit this and instability is the only result. It is occasionally felt essential later that for æsthetic reasons such deformity should be corrected. In such a case an epithelial inlay must be inserted in the region of the scarring to form a pocket into which the prosthesis can be extended without creating a displacing force from the tissues.

Ultimately when healing is complete it is necessary to make a final prosthesis. This may be up to a year from the time of operation, and in the interval adjustments to the original prosthesis are usually necessary. For this reason duplicate prostheses are highly desirable as otherwise the patient has to be without one while this is being done (Figs. 2 and 3).

Unfortunately even when healing is complete it is found that the roof of the cavity is not capable of weight-bearing, and therefore peripheral seal remains the most important factor. It has been found, in fact, that in a large number of cases the extension of a bung into the cavity not only is no aid to stability, but actually, by increasing the weight of the appliance, reduces it.



FIG. 1.—Type of appliance used immediately post-operatively and also frequently as a permanent appliance.



FIG. 2. — Prosthesis with hollow bung extending into cavity.



FIG. 3.—After excision of rodent ulcer with prosthesis showing in cavity. (Operations by R. J. V. B. and W. A. M.)

Attempts have also been made to utilize undercuts by constructing the appliance in two sections inserted separately and united in situ. Not only is the pressure on the undercut not tolerated by the tissues but the additional weight and difficulty of insertion of the appliance are not tolerated by these mostly elderly patients.

In the majority of unilateral cases, therefore, no bung is now used.

Springs between lower and upper dentures can be used to aid stability. When a bilateral removal of maxilla has been undertaken, these are quite satisfactory and in fact usually the only method of obtaining a reasonably stable result. In unilateral cases, however, they are of use only when a pressure-bearing surface is available on the operated side. Otherwise they tend to tilt and displace the appliance instead of maintaining it in position.

Finally, even with ordinary full upper and lower dentures it is frequently impossible to obtain complete comfort with elderly patients wearing them for the first time. Too much must, therefore, not be expected in all these cases from prosthetic replacements.

The President said that in the case of a patient with one of these lesions it was necessary to consider carefully what deformity there would be after an operation for complete removal of the neoplasm.

Mr. E. Musgrave Woodman said that, in his Hunterian Lecture of 1926, he laid emphasis on two important principles in the surgery of this area.

Firstly the fullest exposure possible must be obtained and for this purpose he turned back the face by a paranasal incision commencing above through the eyebrow. Suturing

was by subcuticular silk and a dressing of gold leaf and the resulting scar in a few months was hardly noticeable.

Secondly it was vital to leave a window of inspection so that the operation area could be adequately watched for a recurrence. For this reason he invariably removed the hard palate of the same side and the opening was closed by a dental obturator.

He agreed with Mr. Mill that dislocation of the eyeball could be avoided if the tissues were kept still and fully supported for ten days.

Mr. Mill, in reply, agreed with Mr. Musgrave Woodman that if one wanted to get a really good exposure of the pterygoid region it was advisable to turn back the cheek. He also agreed that if a lateral incision had to be made it was better to make it through the lower conjunctiva and not through the eyelid, because this resulted in œdema. Even if one had to take the roof of the antrum away the eye, as a rule, did not drop and there was no doubt that packing of the cavity afterwards did help to keep the eye up. However, if one had to carry the removal of bone rather higher than usual on the medial and the lateral sides the eye did sometimes drop and he knew no way to prevent this.

Most of the patients he had been discussing had had treatment by radiotherapy before they were operated on. Occasionally with malignant disease of the antrum in older patients excision was carried out first and this was followed by treatment by a radium applicator. There were some old patients who could not face up to a long course of radiotherapy to be followed later by operation and provided the cases were not too extensive they could be treated in this way.

In reply to a question about lymph nodes he said that he did not agree with prophylactic block dissection. He regarded block dissection as causing a certain amount of morbidity in older patients and he thought it was better as a rule to wait until enlarged glands could be felt before advising it.

Before operation biopsies, if necessary multiple, were taken to judge as far as possible the extent of the growth. During operation, especially in cases of extensive rodent ulcers, use was made of the frozen section technique to make as sure as one could that one had excised all the diseased area.

He wished to thank Mr. Warren of Messrs. Clement Clarke and Mr. A. Brook of Queen Mary's Hospital, Roehampton, for their great help with prostheses.

Mr. Battle, also in reply, said with regard to the use of the forehead that one should avoid bringing hair down on to the nose or on to the face. Any hairs introduced in this way could not be removed effectively by irradiation and would have to be removed surgically.

In employing bone grafts for the restoration of contour he used cancellous bone from the ilium. If for any reason bone was contra-indicated, cartilage made a good second best.

Some of the prostheses had been produced by Mr. A. Brook of Roehampton.

[*December* 7, 1956]

A DISCUSSION on **Benign Tumours of the Larynx** was opened by **Mr. F. C. W. Capps** and **Mr. J. P. Stewart; The President, Mr. J. McFarland** and **Mr. S. W. Allinson** also took part in the discussion.

The following clinical records were presented:

Chondroma of the Arytenoid.—Mr. L. F. W. SALMON.

Bilateral Laryngocele (with film).—Mr. G. H. BATEMAN and Mr. J. KODICEK.

Non-Specific Granuloma of Larynx.—Mr. R. SALKELD.

Primary Carcinoma Presenting in Right Nostril—Maxillary Resection with Osteoplastic Restoration of Antrum.—Mr. W. O. LODGE.

Tuberculosis of the Pharynx (Two Cases).—Mr. P. E. ROLAND.

Cerebrospinal Rhinorrhœa Associated with Osteopetrosis.—Mr. A. SEYMOUR-JONES.

The meeting will be reported in the *Journal of Laryngology*.

March 1, 1957]

A DISCUSSION on **The Larynx in Rheumatoid Arthritis** was opened by **Mr. A. Young, Dr. C. S. Darke** and **Dr. L. Wolman.**

Mr. P. Scott, Mr. J. W. S. Lindahl, Mr. H. V. Forster, Mr. J. A. B. Thomas, Mr. T. Levitt and **The President** took part in the subsequent discussion.

Mr. C. P. Wilson read a paper on **Treatment of Choanal Atresia** which was discussed by **Mr. S. W. G. Hargrove, Mr. H. D. Brown Kelly** and **Mr. A. G. Gibb** (to be published in the *Journal of Laryngology*).

Section of Proctology

President—RONALD W. RAVEN, O.B.E., T.D., F.R.C.S.

[*February* 13, 1957]

DISCUSSION ON ARGENTAFFINOMA

Dr. P. S. Macfarlane (Department of Pathology, University of Glasgow, at Western Infirmary, Glasgow): *The Pathology of Argentaffinoma: The Use of 5-HIAA Estimation in Diagnosis*

Pathology.—A brief review of the pathological features of argentaffinomata or carcinoids is justified by the recent interest which has been aroused in these uncommon tumours by the discovery that they secrete 5-hydroxytryptamine (5-HT). An excess of this substance in the circulation is responsible, in some cases, for a striking clinical syndrome (Biörck *et al.*, 1952; Thorson *et al.*, 1954).

Incidence.—The tumours are most commonly encountered in the appendix but in this situation they are usually of no great importance since they are removed when too small to cause endocrine effects and to metastasize. Although these tumours have been reported throughout the alimentary tract, in the gall-bladder, biliary passages, pancreas, and in ovarian teratomata, the most common site outside the appendix is the ileum where they are often multiple.

Carcinoids occur at all ages except in the appendix where juveniles are usually affected. In my own series of non-appendicular cases the age extremes are 19 years and 83 years. It should be remembered, however, that the slow growth of these tumours probably vitiates the correct assessment of age incidence.

Ætiology.—The tumours have not been produced experimentally and there is no evidence of any external carcinogen being involved. The facts, that they occur at an early age and that they have been associated in some instances with developmental anomalies elsewhere in the body (Spain, 1955), have been used to support the view that carcinoids are developmental tumours. Many cases do, however, satisfy the usual criteria of malignant neoplasia and this interpretation seems the most reasonable at the moment.

Histogenesis.—The tumours are generally considered to arise from the argentaffin (or Kulschitsky) cells of the alimentary tract. These cells lying deep in the crypts are seen, after formalin fixation, to contain granules which characteristically give the following main histochemical reactions: (1) they spontaneously reduce silver salts; (2) they give a striking orange colour with the diazonium reaction (Pearse, 1953) this method has been found most useful in routine practice; and (3) they fluoresce brilliantly in ultraviolet light. By histochemical methods Barter and Pearse (1955) have shown that the Kulschitsky cells almost certainly contain 5-hydroxytryptamine in some form.

Appearances.—In the ileum the commonly encountered features are multiplicity, a yellow colour, a tendency to occupy the submucous layers without ulcerating into the lumen and, frequently, an association with a greater amount of hypertrophy of the bowel muscle than might be anticipated on the basis of mechanical obstruction alone. The naked-eye characters are not diagnostic and recourse must be made to microscopy in many cases. Dukes (1946) has shown that most of the carcinoids in the rectum and colon are benign and mimic in appearance the more common simple neoplasms of the region, often presenting as sessile projections into the lumen. In contrast, Gabriel and Morson (1956) have described a deeply ulcerating argentaffinoma of the rectum with lymphatic and liver metastases.

Histology.—In the majority of cases the morphological features are characteristic. The cells are in compact, rounded, aggregates often showing a tendency to peripheral palisading. Tubular and acinar formations are usually not prominent. With hæmalum and eosin staining the round uniform nuclei show a characteristic fine dusting of the chromatin while the specific granules, in highest concentration in the peripheral cells of the aggregates, are eosinophilic. Positive results are usually obtained with the histochemical reactions already mentioned. Some cases may lack these characteristics, however, and histological diagnosis, even with the special stains, may be difficult or impossible. Gabriel and Morson (1956) suggest that the large bowel carcinoids are somewhat different from those occurring at other sites in that they show poorer specific granulation and have a tendency to form tubules and acini.

Criteria of malignancy and metastases.—The smallest tumours show infiltrative features and often local lymphatic permeation but again the characteristic slowness of growth means that, in practice, the majority behave in a benign fashion despite the histological indications of malignancy. This is true particularly of the appendicular and large intestinal sites. The ileal carcinoids often have metastasized to the local lymph nodes and even to the liver, by the time laparotomy is done, but in such cases, the slow growth of the metastases is often so prominent a feature that very long survival periods are the rule.

Transcœlomic spread to the ovaries and also systemic dissemination to bones and other organs occur.

Studies on the excretion of 5-hydroxyindole acetic acid (5-HIAA) in cases of argentaffinoma.—5-HT is derived from the essential amino acid tryptophan and is broken down by the widespread enzyme amine oxidase to give 5-HIAA. The greater part of 5-HT formed in the body is excreted as 5-HIAA which can be comparatively simply estimated in the urine. The normal excretion is within the range of 3–14 mg./24 hours. Determination of urinary 5-HIAA has proved a useful method for detecting 5-HT over-production, and several cases have been studied (Macfarlane *et al.*, 1956).

Table I summarizes the findings in cases of argentaffinoma in which it was known that

TABLE I.—PROVED ARGENTAFFINOMATA

Case No.	Clinical			Site	Excretion of 5-HIAA (mg./24 hours)
	Flushing	Pulmonary stenosis	Diarrhœa		
1	−	−	±	Small bowel and liver	688 594
2	+	−	−	Ileo-cæcal and mesentery NOT liver	155
3	+	−	±	Ileum and mesentery NOT liver	65 90 84
4	++	+	+	Ileum, mesentery and liver	258 269
5	−	−	−	Ileo-cæcal and mesentery NOT liver	43

tumour tissue had not been eradicated by operation. The urinary excretion of 5-HIAA is significantly increased in them all and yet this is not associated with any constant clinical picture or with a particular distribution of tumour tissue. The findings, however, indicate that the assay of urinary 5-HIAA is useful in diagnosis.

Table II summarizes the findings in several cases in which the diagnosis of argentaffinoma seemed possible. Case 6 is particularly interesting and has been reported elsewhere (Smith *et al.*, 1957). In it the high urinary excretion of 5-HIAA confirms the tentative clinical diagnosis of argentaffinoma in spite of negative histochemical tests on tumour material from the liver and a bony metastasis. The latter tissue was, however, shown to contain a high content of 5-HT.

In the other cases in Table II the normal excretion of 5-HIAA, of course, suggests that they are not cases of argentaffinoma.

TABLE II.—THE DIAGNOSTIC USE OF 5-HIAA EXCRETION

Case No.	Clinical data	Pathology	Excretion of 5-HIAA (mg./24 hours)
6	Flushing ++ Secondary tumours in liver and bone Primary not known	Histology not clearly argentaffinoma Specific stains negative	140
7	Subacute intestinal obstruction: surgical diagnosis carcinoid	Biopsy inadequate	11·2 9·1
8	Multiple colonic tumours	3 adeno-carcinomata 1—? argentaffinoma Specific stains—negative	11·3
9 10 11	Cases of flushing and cyanosis of unknown origin	—	less than 10
12	Spasmodic flushing: Mass in right iliac fossa	—	5·2

The assay of 5-HIAA in urine is also indicated in cases of argentaffinoma after surgical treatment, but in such circumstances the sensitivity of the test, in terms of its ability to indicate early metastatic growth, has not yet been established.

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Mr. Adam N. Smith (Department of Surgery, University of Glasgow, at Western Infirmary, Glasgow). (*See Scot. med. J.* (1957), **2**, 24.)

We (Smith *et al.*, 1957) have recently had the opportunity of examining the humoral effects of 5-hydroxytryptamine (5-HT) in 7 cases of metastasizing ileal argentaffinoma. The cases were showing in whole or in part the striking clinical picture of flushing with cyanosis, diarrhœa, cardiac defects and occasional asthmatic-like attacks, now well recognized since its description by the Swedish workers from Malmö. All the cases were excreting very large quantities of 5 hydroxyindole acetic acid (5-HIAA), the oxidation product of 5-HT and numerous other indole compounds (Macfarlane *et al.*, 1956; Dalgliesh, 1956).

A. Metabolism of 5-HT in relationship to tryptophan nicotinic acid and dietary protein and fat

(*i*) *Tryptophan and protein.*—Normal individuals excrete 2–10 mg./day 5-HIAA: true endogenous 5-HT production is probably higher 10–20 mg., requiring a similar amount of tryptophan as precursor. The tryptophan intake of a normal adult is usually 500–1,000 mg./day, greatly in excess of the amount required for 5-HT formation. In cases of argentaffinoma excreting up to 500 mg./day, a major part of the tryptophan metabolism may be utilized in the pathway of 5-HT formation. The metabolic aspects of one case were examined in detail by Drs. C. E. Dalgliesh and R. W. Dutton as follows:

On a protein intake of 82 grams/day the patient was in positive nitrogen balance. Nitrogen balance became negative on reducing protein intake to 31 grams/day; it was not restored by adding 500 mg. *L*-tryptophan/day to the 31 grams protein diet, but returned to its previous positive value on returning to the 82 grams protein diet. The negative nitrogen balance was therefore not due to a simple tryptophan deficiency. On the 82 grams/day protein diet, mean 5-HIAA excretion was 312 mg./day. This dropped to a mean of 224 mg./day on the 31

grams/day protein diet, rose to a mean of 301 mg./day on supplementing the diet with 500 mg. *L*-tryptophan and returned to a mean of 222 mg./day on returning to the low protein diet. The 500 mg. *L*-tryptophan/day added to the diet corresponded to the estimated tryptophan content of the 51 grams/day drop in protein content of the diet between the two stages. Of this 500 mg. tryptophan, approximately one-fifth appeared as urinary 5-HIAA. It follows that a larger amount than this was probably metabolized by the 5-HT pathway. On the low protein diet the tryptophan intake was only of the order of 300–400 mg./day and probably more than two-thirds of this was metabolized by the 5-HT pathway.

These findings are best explained by assuming that the tumour has a basic rate of production of 5-HT, and will draw on circulating plasma tryptophan till this basic production is satisfied. Increase in available tryptophan may increase the rate of production of 5-HT by the tumour slightly, but not in proportion to the increased availability. Until the basic tumour production of 5-HT is satisfied the tumour may exert priority for available circulating tryptophan over protein biosynthesis and at low levels of protein intake an argentaffinoma may seriously impair the nutritional status of a patient.

(*ii*) *Nicotinic acid deficiency.*—Tryptophan is a precursor of nicotinic acid. If excess production of 5-HT by tumour tissue were to take priority for available supplies of tryptophan over protein synthesis and nicotinic acid formation, a serious nutritional deficiency might result. In fact pellagra-like symptoms have been claimed in this syndrome (Thorson *et al.*, 1954; McNeely and Jones, 1946). One of our cases showed symptoms which could well be those of nicotinic acid deficiency. She had had diarrhœa intermittently for two to three months. Another patient complained of recurrent mouth ulcers with violet discoloration of the extremities.

The average diet in this country contains enough tryptophan to supply large demands by a tumour for 5-HT synthesis and yet still have enough for ordinary protein anabolism and nicotinic acid synthesis as well. In addition, patients with argentaffinomatosis may have diarrhœa and it seems likely that this may be important as a cause of the deficiency.

(*iii*) *Evidence for alimentary control of release of 5-HT by fat, &c.*—Bleehen (1955) claimed that a fatty meal in his patient not only caused flushing but also raised the excretion of 5-HIAA. The time relations were such that a direct effect on the tumour of the products of absorption seemed unlikely: what seemed probable was the production in the stomach or duodenum of some intermediate hormone liberating 5-HT. It seemed important to confirm Bleehen's findings since by analogy it could be postulated that the discharge of 5-HT by the normal argentaffin cell might depend on a similar stimulus.

Four patients were placed on a high fat diet for five days each. There was a substantial fall in 5-HIAA excretion and it is thus disappointing not to be able to confirm Bleehen's observation.

B. Trial of antagonists and 5-HT releasing agents

Brominated lysergic acid (B.O.L.) (Cerletti and Rothlin, 1955) antagonizes 5-HT without the disturbing effects on cerebral function of the other related drugs.

It had little effect clinically on our cases; in one case there appeared to be a definite diminution of 5-HIAA excretion. Continuous administration of reserpine provoked an overall increase in frequency and intensity of flushes and frequency of bowel movements. There was a marked rise of 5-HIAA, followed by a fall in 5-HIAA excretion indicating a period of relative depletion in the tissues. This agent may prove useful as a provocative test in the non-secreting cases.

C. Blood and urinary levels of 5-HT and related compounds

Despite rapid conversion to 5-HIAA, a high blood level of 5-HT was found in all secreting cases (1–3·2 μg./ml.: normal range 0·08–0·6 μg./ml.). Despite the large numbers of indole compounds in the urine, in the typical case, 5-HT itself is not present or detectable, nor is the precursor 5-hydroxytryptophan (5 Htp). In one exceptional case with multiple metastases 5-HT and 5 Htp were both present in considerable amount in the urine. This represents a striking confirmation for the human subject of the accepted biochemistry of the condition, precursor, active substance and breakdown product having presumably "leaked out" together into the urine from a renal metastatic site.

D. Finally a unique feature of the syndrome must surely be its protean nature; our cases presented as, or could have been confused with, subacute intestinal obstruction with diarrhœa, ulcerative colitis, Raynaud phenomenon, cardiac defects, multiple sarcomata, oliguria and menopausal flushing.

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Mr. I. S. R. Sinclair (Department of Clinical Surgery, University of Edinburgh):

Some Aspects of Intestinal and Renal Function in Metastasizing Argentaffinoma

The striking humoral effects associated with argentaffinomata are found only when metastasis has occurred and are even then inconstant. At a stage when total eradication of

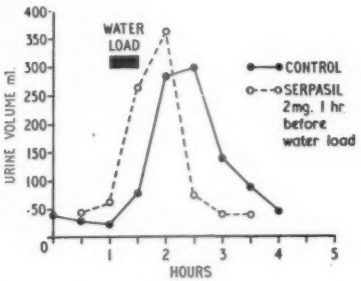


FIG. 1.—Diuretic response to intravenous water load in normal subject before and after intramuscular injection of reserpine.

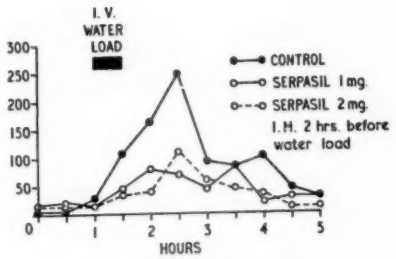


FIG. 2.—Diuretic response to intravenous water load in patient with metastasizing argentaffinoma before and after intramuscular injection of reserpine.

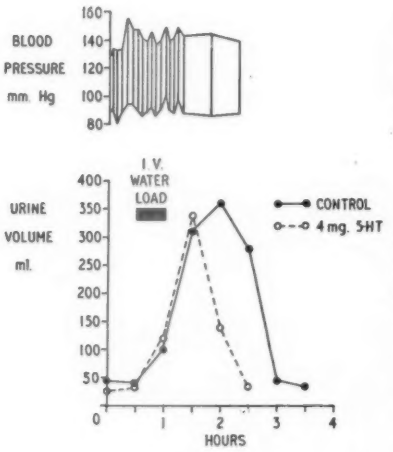


FIG. 3.

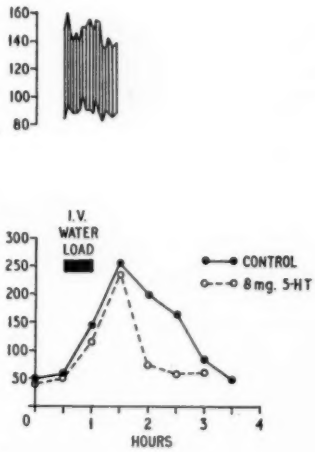


FIG. 4.

FIGS. 3 and 4.—Effect of intravenous infusion of 5-hydroxytryptamine on maximal water diuresis in normal subject. (5-hydroxytryptamine given simultaneously with intravenous water load.)

the tumour may be achieved by surgery we must rely for diagnosis on the local effects of the primary tumour. In the commonest site of occurrence—the appendix—these tumours are almost invariably associated with obliteration of the lumen, although the exact relationship of the tumour to the obstruction is not entirely clear. Symptoms of appendicular colic or of appendicitis are usually present and cause the patient to have appropriate treatment before metastases have occurred. In the rectum, obstructive symptoms are rare but in more than half of the reported cases without evidence of metastases there have been abdominal symptoms that have directed attention to the rectum. The commonest single complaint has been rectal bleeding, in contrast to the rarity of hæmorrhage from carcinoid tumours in

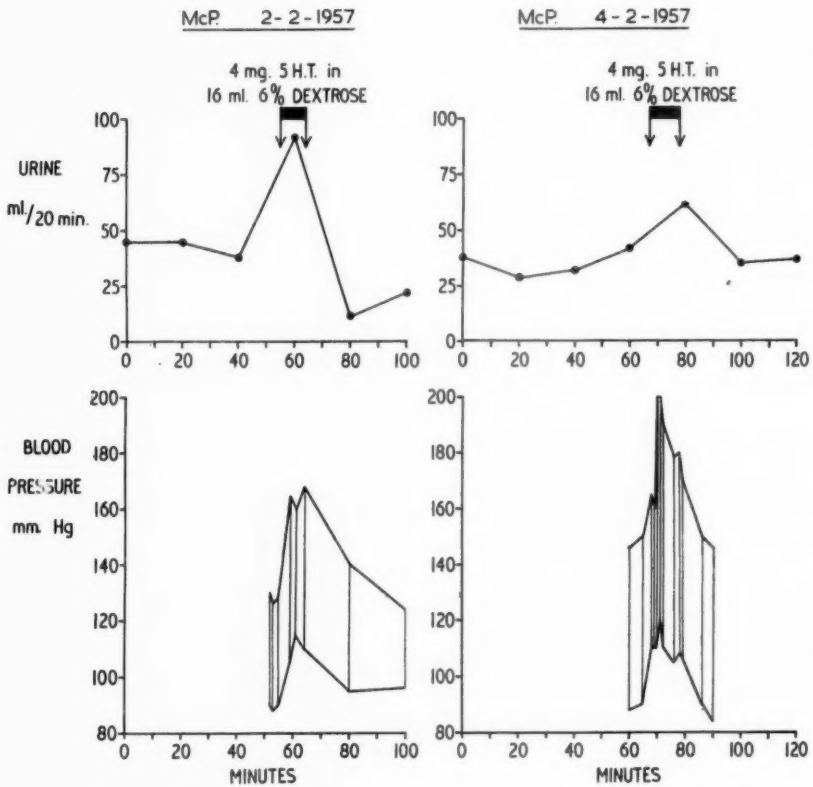


FIG. 5.—Effect of intravenous injection of 5-hydroxytryptamine on urine flow in normal subject under constant conditions.

other sites. The other principal symptoms have been rectal pain and some alteration in bowel habit.

The number of rectal carcinoids reported has more than doubled since the Section was addressed on this subject in 1950 by Mr. R. W. Raven, and the high proportion of symptomless, non-metastasizing carcinoids reported in this situation probably reflects the greater accessibility of the rectum rather than a lesser tendency towards malignancy. The most important group of tumours are those occurring in the small bowel. As with other small bowel neoplasms symptoms of disturbed intestinal function are of relatively late occurrence, and although the symptoms and signs of partial obstruction were present in almost two-thirds of 200 cases from the literature for which adequate clinical data are available,

metastases were already present in two-thirds of this obstructed group. Therefore, although argentaffinomata are particularly liable to cause intestinal obstruction, this tendency is not great enough to enhance the likelihood of early diagnosis.

Diarrhœa is less common than obstruction, being present in only one-quarter of the series of small bowel carcinoids reviewed, but is of more sinister import than obstruction in that of the 52 cases with diarrhœa all but 4 had metastases and most had hepatic as well as nodal secondaries. This suggests a predominantly humoral causation.

The characteristic feature of intestinal function in this syndrome is continuous activity of the gut. The increased motility is unrelated to the presence of obstruction and in the presence of widespread metastases continues after resection of the primary tumour. Increased

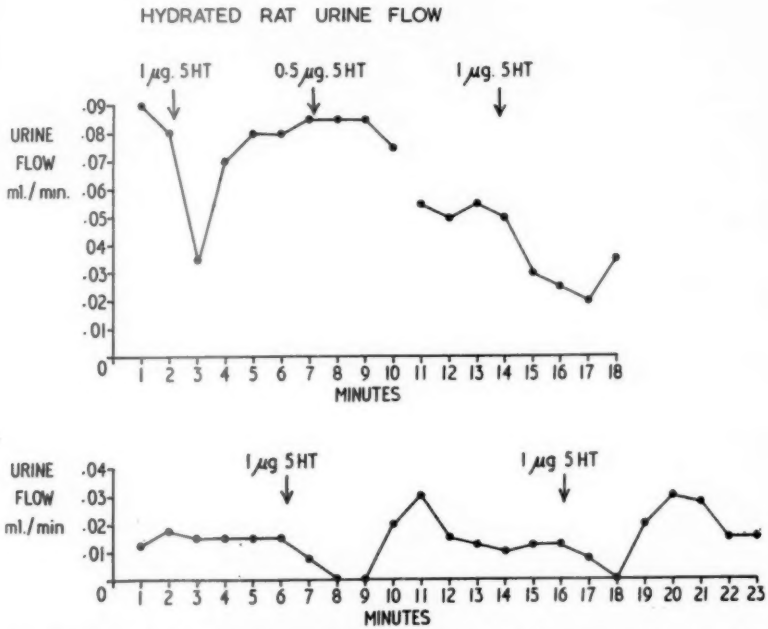


FIG. 6.—Effect of instantaneous intravenous injection of 5-hydroxytryptamine on urine flow of alcohol-anæsthetized hydrated rat. Injected dose given in 1 ml. isotonic saline.

borborygmi are present even in the absence of diarrhœa. Although typical, this excessive activity is by no means pathognomonic. A test which may ultimately prove to be more selective in patients having an unusually active gut depends on the effect on the intestine of ganglion-blocking agents such as hexamethonium bromide. From preliminary observations it seems likely that in individuals with hypermotility of the gut from various causes other than an excess of 5-hydroxytryptamine, peristalsis can be temporarily arrested by doses of these drugs that will not abolish peristalsis in patients with argentaffinomata. This is in keeping with the work of Robertson (1953) and of Rocha e Silva and Ribiero do Valle (1953) who showed that hexamethonium does not antagonize, and may even augment, the effect of 5-hydroxytryptamine on the guinea-pig ileum.

The occasional association of pellagra with the syndrome of metastasizing argentaffinoma has been noted. Of the 5 patients with this syndrome whom I have seen, none has had severe diarrhœa and none has shown any evidence of nicotinic acid deficiency. The patient with severe pellagra and metastasizing argentaffinoma recorded by McNeely and Jones (1946) was passing up to 20 stools daily. One of the cases reported by Smith *et al.* (1957) showed signs and symptoms compatible with pellagra and this patient had suffered from diarrhœa for several months. It seems likely that the diarrhœa rather than the metabolic parasitism of the tumour is the principal factor in the development of a deficiency state. It is possible,

too, that 5-hydroxytryptamine may prove to have some more direct relation to pigment metabolism than through its occasional association with pellagra.

A patient of Sir James Learmonth with an abdominal mass which proved to be a metastasis from an ileal carcinoid had a daily urine output of from 500 ml. to 700 ml. in the absence of any evidence of fluid retention. This observation, in the light of Erspamer and Ottolenghi's (1952) work in which they found 5-hydroxytryptamine to be highly antidiuretic, first led me to suggest that disturbances of renal function and, in particular, periodic oliguria, might constitute yet another facet of this syndrome. A search of the literature lent scant support to this idea. In the few cases where urinary findings have been recorded they have been unremarkable except in some rare instances of direct involvement of the urinary tract by the pathological process, as in the classical case shown by Sir Maurice Cassidy in 1930. The solitary exception to this statement is the case reported by Snow *et al.* (1955) in which attacks of flushing and weakness were associated on at least one occasion with complete anuria lasting for four hours. In April 1956 I had the opportunity of visiting Professor Waldenström's clinic in Malmö where the significance of the syndrome was first recognized (Thorson *et al.*, 1954), and found that a number of their patients had showed periods of oliguria lasting for five or six days during which the urinary output approached the "volume obligatoire". A similar observation has recently been reported by Smith *et al.* (1957). There does not seem to be any correlation between severity of symptoms and the occurrence of oliguria although in Smith's cases the oliguria was noted in the 2 patients having the most severe vasomotor manifestations. Renal function tests carried out in the 5 cases available to me have not disclosed any particular deviation from normal except in 1 patient with right ventricular failure.

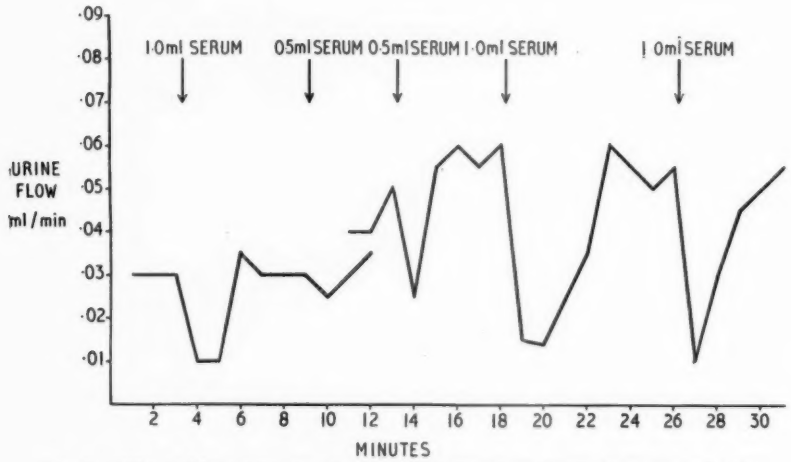


FIG. 7.—Effect of instantaneous intravenous injection of serum from patient with metastasizing argentaffinoma on urine flow of alcohol-anæsthetized hydrated rat.

To investigate further the possible antidiuretic activity of 5-hydroxytryptamine in man, I observed the effects on maximal water diuresis of reserpine, which is believed to release 5-hydroxytryptamine, and later of 5-hydroxytryptamine itself. The technique used was the rapid intravenous infusion of isotonic dextrose in a volume equal to about 2% of the total body water (in practice about 850 ml.). Urine was collected at thirty-minute intervals throughout the experiment. Whereas in normal subjects an intramuscular injection of reserpine in doses of 1 mg. to 2 mg. given one or two hours before the test did not modify the diuretic response in any way (Fig. 1), the same test in patients suffering from metastasizing argentaffinoma revealed a consistent reduction in the total response (Fig. 2). It was not possible to detect any significant change in the urinary output of 5-hydroxyindole acetic acid as a result of the injection of reserpine in this dosage.

The dose of 5-hydroxytryptamine which can be given by intravenous injection in man is limited by the unpleasant subjective sensations (tightness in the chest, flushing and tingling and increased bowel and bladder activity) and by the development of extrasystoles. When

doses up to the limit of tolerance were given by slow intravenous injection simultaneously with a water load in normal subjects no significant modification of the pattern of diuretic response was observed although the duration of diuresis tended to be shortened (Figs. 3 and 4). Because inhibition of a maximal water diuresis requires very great antidiuretic activity the effects of 5-hydroxytryptamine were tested during constant secretion at lower rates. The response was negative (Fig. 5).

In view of these equivocal results the earlier experimental work was reviewed. Most of this work was based on the subcutaneous injection of the test substance in conscious rats (Erspamer and Ottolenghi, 1952). Not only are subcutaneous injections unreliable in the assay of antidiuretic activity but 5-hydroxytryptamine tends to be extremely painful when injected, and any painful stimulus will produce powerful antidiuresis. In the only reported experiments in which intravenous injections of 5-hydroxytryptamine have been given to anæsthetized rats antidiuresis was not observed (Ames and Van Dyke, 1952). In these experiments urine collections were made at ten-minute intervals, and it appeared worth while to repeat this work using more sensitive methods. This was done in conjunction with Mr. H. A. F. Dudley, using a modification of the method described by Jeffers *et al.* (1942). The test substance is injected into the femoral vein of the alcohol-anæsthetized hydrated rat, the rate of urine flow being measured by the rate of advance of the meniscus along a micropipette attached to a cystostomy tube after ligature of the urethra. In this highly sensitive preparation the effect of 5-hydroxytryptamine was constant and reproducible (Fig. 6). Within ten seconds of injection there was a sharp drop in the rate of urine flow but this effect always passed off within three minutes. Moreover, whereas serum from a normal individual did not have any effect on this preparation, serum from a patient with metastasizing argentaffinoma had an effect comparable to that produced by 5-hydroxytryptamine (Fig. 7).

The doses of 5-hydroxytryptamine necessary to produce this transitory effect (in the order of 0·5 μg./100 grams) were comparable to those found by Erspamer and Ottolenghi (1953) to have a prolonged and profound antidiuretic effect.

Taken in conjunction with Abrahams' and Pickford's (1956) carefully controlled studies which failed to disclose in dogs any antidiuretic effect from doses of 5-hydroxytryptamine which did not also produce marked reflex disturbances of respiration and vasomotor activity, these results suggest that Erspamer's (1954, 1955) concept of 5-hydroxytryptamine as a specific renal hormone is unlikely to be correct. Whether the occasional periodic oliguria observed clinically is related to a direct effect of 5-hydroxytryptamine remains for the present uncertain.

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Dr. J. **Boyland** and Dr. D. C. **Williams** (Chester Beatty Research Institute, Institute of Cancer Research: Royal Cancer Hospital, London): ***Tryptophan Metabolism in Patients with Carcinoid and Other Tumours***

The characteristic biochemical abnormality of argentaffinomas is the conversion of tryptophan to 5-hydroxytryptamine or serotonin. Many bacteria convert tryptophan into indole

which at one time was thought to play a role in intestinal cancer, but this is still uncertain. Indolylacetic acid, which is produced from tryptamine, is the plant growth hormone auxin B. In cases with a rare metabolic disease, Hartnup disease, indolylacetic acid is excreted to such an extent that a shortage of tryptophan for nicotinic acid formation occurs (Baron *et al.*, 1956). The ensuing nicotinic acid deficiency is often associated with pellagra-like symptoms. Patients with Hartnup disease resemble those with carcinoids in that they sometimes develop pellagra-like symptoms.

The major metabolic pathway of tryptophan in normal mammals leads through kynurenine, 3-hydroxykynurenine 3-hydroxyanthranilic acid to nicotinic acid. We have been particularly interested in this process because 3-hydroxyanthranilic acid is carcinogenic when implanted in the bladders of mice and it may be a cause of cancer of the bladder in man (Allen *et al.*, 1957). A subsidiary metabolic route involving 3-hydroxykynurenine leads to formation of xanthurenic acid—a substance which is said to induce hyperglycæmia and may be important in diabetes.

Our own approach to the carcinoid problem has been through interest in those tryptophan metabolites which may be of importance in cancer of the bladder. We (Boyland *et al.*, 1956) have developed a method in which some 16 tryptophan metabolites were separated on paper chromatograms and their amounts estimated by the measurement of the areas of the spots produced by the different substances.

In most of the patients twenty-four-hour specimens of urine, collected under normal conditions and following administration of 2 g *L*-tryptophan, were examined. The administration of tryptophan reduces the variation in tryptophan intake due to differences in diet and increases the amounts of the metabolites excreted, so that abnormalities in excretion patterns are more easily seen.

The method applied to 3 patients with carcinoids gave results similar to those found by other workers. The urine of these patients did not contain abnormal amounts of any of the other possible tryptophan metabolites including anthranilic acid, 3-hydroxyanthranilic acid, 5-hydroxyanthranilic acid, 3-hydroxyanthranilic acid sulphuric ester, kynurenine, 3-hydroxykynurenine, tryptamine, and indoxyl sulphate.

The same tryptophan metabolites have been determined in the urine of patients with tumours of different sites. Patients with bladder cancer excrete increased amounts of 3-hydroxyanthranilic acid and 3-hydroxykynurenine (Boyland and Williams, 1956). In investigation of these substances it was found that patients with carcinomata of the vocal cord, pyriform fossa or bronchus excreted somewhat more 5-HT or 5-HIAA than did other patients, following administration of 2 g *L*-tryptophan. The amounts excreted were small compared with those of carcinoid patients but more than excreted by patients with cancer of the bladder or cancer of the breast or by subjects free of malignant disease. Excretion of 5-HIAA by a patient with cancer of the bronchus has recently been described by Harrison *et al.* (1957). The administration of *L*-tryptophan to subjects before the collection of urine for examination undoubtedly increases the possibility of detecting metabolic abnormalities.

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Professor D. F. Cappell (Department of Pathology, University of Glasgow, at Western Infirmary, Glasgow) commented on the notable hypertrophy of the smooth muscle of the ileum at the site of an argentaffin tumour and suggested that this might be attributable to a local effect of serotonin liberated by the neoplasm. Ileal carcinoids were, in his experience, usually multiple and very commonly spread to the mesenteric nodes and liver, whereas he had not seen a rectal carcinoid spread in this way. With regard to the case described by Drs. Macfarlane and Smith, he had studied the histology of the metastatic deposit in the humerus, and confirmed that in spite of its secretory activity it lacked the spceific histological characters that one associated with argentaffinoma.

Section of Endocrinology

President—T. Russell Fraser, M.D., F.R.C.P., D.P.M.

[*January* 23, 1957]

DISCUSSION ON AMENORRHŒA AND HIRSUTISM

Dr. J. H. Rey:

Amenorrhœa and Psychiatric States

The problem of menstrual disorders in psychiatric illnesses is of interest from at least two aspects. Firstly, there is a higher incidence of amenorrhœa, irregular cycles, and irregular length and amount of bleeding in mental patients than in any other groups (Hanse, 1923; Ripley and Papanicolaou, 1942; Strachan and Skottowe, 1935). Also, there are certain abnormalities of behaviour and changes in mental state coinciding with certain phases of the cycle, e.g. premenstrual depression, higher incidence of suicides, delinquency, &c., in the luteal or premenstrual phase (Kroger and Freed, 1951; Mackinnon and Mackinnon, 1956; Rees, 1953). Further, certain psychiatric illnesses sometimes follow a periodic course parallel to the menstrual cycle, e.g. periodic catatonia. Secondly, little is known of the mechanisms by which the menstrual disturbances become operative. Since it is well authenticated that certain types of disorder such as amenorrhœa can follow on an emotional disturbance (Kroger and Freed, 1951), presumably some psycho-physiological mechanism possibly functioning at the hypothalamic-pituitary level is involved in the process. Such a hypothesis was put forward by Reifenstein (1946) to explain his findings in so-called cases of "psychogenic" or "hypothalamic" amenorrhœa. A number of conditions had to be fulfilled for this syndrome to be diagnosed. There should be a history of psychic trauma preceding the amenorrhœa, normal gonadotrophin excretion, defective œstrogenization of the endometrium and vaginal mucosa, failure of bleeding after progesterone administration and withdrawal bleeding following œstrogen therapy. He suggested that the defective factor was the absence of the lutein stimulating hormone which was suppressed at the hypothalamic level. However, very few endocrine studies indeed are available as to the endocrine status of psychiatric patients with functional menstrual disorders.

Objects of the Experiment

The present study was designed to investigate this problem. The investigation covered 22 patients below age 45 suffering from secondary amenorrhœa of more than two months' standing; 8 patients with irregular bleeding below age 45; 8 patients with amenorrhœa or irregular bleeding above age 45; 20 patients suffering from puerperal psychoses with amenorrhœa; and, finally, a group of 9 patients with regular periods.

Methods

Gonadal activity was assessed by daily examination of vaginal smears and cornification index counts over periods of not less than a month and up to several months in most cases. Repeated gonadotrophin estimations were done using the ultrafiltration technique; urinary 17-ketosteroids excretion was also assessed as well as the measurement of thyroid activity using the I^{131} urinary excretion method.

Findings

A. *Vaginal Smears*

(1) *Secondary amenorrhœas.*—The smears showed: (*a*) protracted phases of low and defective œstrogenization as indicated by a low cornification index, the "dirty" type of smears with small cells, debris, leucocytes and sometimes basal cells; (*b*) absence of clearly-defined progesterone effect; (*c*) absence of ovulatory smears; (*d*) presence of fluctuations in the cornification index but no regular cyclical activity; (*e*) sharp contrast with the picture found in normal cycles.

(2) *Irregular menstruation.*—Tendency to show a protracted and defective follicular phase, delayed or absent ovulation, absence of well-established progesterone effect.

(3) *Puerperal amenorrhœas.*—The smears resembled those of the secondary amenorrhœas but basal cells were more often present and in higher percentages.

(4) *Amenorrhœa and irregular bleeding above age* 45.—Two types of cases were observed: (*a*) those with a high and well-sustained cornification index but no signs of progesterone activity; (*b*) those resembling cases below age 45.

B. *Gonadotrophins*

Urinary gonadotrophin estimations showed fluctuations in the same patients from low to normal levels. Normal values were obtained for a control group of 16 psychiatric patients with regular menstrual cycles. A comparison was made between the first values obtained in the cases of amenorrhœa and irregular menstruation below age 45 and values for the psychiatric control group. The tendency to lower activity in the abnormal group was significant at the 1% level, with a mean of 6·2 m.u. for the abnormal group and 16·3 m.u. for the control group. The group of patients above age 45 showed an increased gonadotrophin activity.

C. 17-*Ketosteroids*

Repeated estimations showed fluctuating levels of excretions. A comparison of first estimations made between abnormal groups and psychiatric controls showed that for both the amenorrhœas and cases of irregular bleeding below age 45, but not the puerperal patients, there was a tendency to lower levels of excretion significant at the 1% level. The mean for the amenorrhœas and cases with irregular menstruation was 6·3 mg./twenty-four hours and that for the psychiatric control group was 9·4 mg./twenty-four hours.

D. *Thyroid Activity*

30 patients with abnormal periods or amenorrhœa were compared with a group of 24 patients with normal menstruation by the I^{131} urinary excretion test. There was no significant difference between the groups though the scatter was significantly greater in the case of the abnormal group. The distribution curve for "T" showed a slight shift to the region of low uptake for the abnormal group when compared with the psychiatric controls.

Discussion

These results can be compared with previous endocrine findings in non-psychiatric cases of functional amenorrhœa and oligomenorrhœa and with studies on psychiatric patients with similar disturbances.

With regard to the first group, the commonest abnormal finding is that of a low level of œstrogen excretion, though normal levels can be found and high levels seldom (Pedersen-Bjergaard and Tonnersen, 1951; Ripley and Papanicolaou, 1942). Gonadotrophin estimations are more often reported as being normal or low, or occasionally high (Albert, 1957; Pedersen-Bjergaard and Tonnersen, 1951). Few studies have been made of the full endocrine picture of these patients. Similarly, reports about œstrogen and gonadotrophin excretion often refer to single estimations. With regard to the gonadotrophins, this is looked upon as a serious drawback by Albert (1957) in his thorough review of the subject as daily fluctuations and rhythmical variations may exist even in amenorrhœa. As to vaginal smear findings, Allende and Orias (1950) report similar findings to those of the present study.

With regard to psychiatric studies, Reifenstein's hypothesis has been referred to. Ripley and Papanicolaou (1942) studied the menstrual cycles in mental patients suffering from psychoses. They did serial vaginal smear examinations and found the commonest abnormality was an atypical follicular reaction and a delayed follicular phase indicating subnormal œstrogen activity. They concluded that there was a delay in development and maturation of the follicle resulting in delayed ovulation, prolonged cycle or amenorrhœa. There was a positive relationship between severity of illness and degree of ovarian function. They declined to offer a suggestion as to the missing factor. Undernutrition was not a factor. This can also be eliminated in the present study, except in the cases of anorexia nervosa, though the menstrual disturbance is known often to precede the loss in weight in these patients.

Summary and Conclusion

In this study patients suffering from secondary amenorrhœa and irregular menstruation showed absence of ovulation, absence of progesterone activity, and defective follicular activity in the smears. There was some indication that gonadotrophic activity, 17-ketosteroids excretion and perhaps thyroid activity tended to be on the low side of normal

and differed significantly from comparative measurements in a control group. It was not possible to demonstrate whether defective gonadal activity was due to the absence of a lutein stimulating hormone, as this could not be measured. However, the above findings are in favour of a hypothesis that there is a hypothalamic-pituitary participation. The fluctuations observed over extended periods of time, and often in connexion with changes in the mental state, explain the various findings reported by different workers. It also shows that the intensity of the degree of dysfunction may vary, the gonadotrophins being the most sensitive to the disturbing process (Hubble, 1955).

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Dr. B. T. Donovan:

The Hypothalamus and Gonadotrophin Secretion

Although many cases of psychogenic amenorrhœa have been described, knowledge of the mechanisms underlying this condition would seem to have advanced little beyond the suggestion of Klinefelter *et al.* (1943) that there is a disturbance of the release of luteinizing hormone (LH). This view was derived, in part, from the information then available concerning the hypothalamic control of gonadotrophin secretion in laboratory animals, and since considerable advances have been made in this field in recent years it may be useful to sketch very briefly some of the more recent findings.

It is now clear that LH may be released from the pituitary gland by electrical stimulation of the hypothalamus. This response is particularly well shown in the œstrous rabbit by the occurrence of ovulation some ten hours after the stimulus and has been described by Harris (1937, 1948), Haterius and Derbyshire (1937), Markee *et al.* (1946), and Kurotsu *et al.* (1950). Collateral evidence for the participation of neural factors in the release of LH in other species has also been produced. The blockade of ovulation in the rat (Everett, 1952), the advancement of ovulation by coitus in the cow (Marion *et al.*, 1950), the modification of œstrous cycle length by uterine distension in the ewe (Nalbandov *et al.*, 1955), and the blockade of ovulation in the hen (van Tienhoven *et al.*, 1954) may all be cited as examples of the investigations which have been made.

Certain consequences of the destruction of localized areas of the hypothalamus may be interpreted in terms of an interference with the release of LH. Dey *et al.* (1940) and Dey (1943) found that destruction of a large area of the hypothalamus immediately posterior to the optic chiasma sometimes produced a state of constant œstrus in guinea-pigs. Ovulation did not occur and the ovaries contained only large follicles. This result was subsequently confirmed in the rat by Hillarp (1949) and Greer (1953) who used rather smaller lesions in the neighbourhood of the paraventricular nuclei. It appears from these experiments that although ovulation was suspended some LH was being released from the pituitary glands of the constantly œstrous rats because the interstitial cells of the ovaries did not show the changes indicative of lack of LH. Greer (1953) also made the observation that progesterone given daily was able to produce ovulation in rats displaying constant œstrus and permit the resumption of œstrous cycles. The finding that smaller doses of progesterone, below those producing ovulation, still were able to interrupt the persistent œstrus of rats with hypothalamic lesions led Alloiteau (1954) to postulate that the steroid inhibited the release of follicle stimulating hormone (FSH). This worker believed that the œstrogen level in the rat made constantly œstrous was insufficient to block the secretion of FSH. Flerkó (1954) has shown that hypothalamic lesions which produce constant œstrus in rats interfere with a feed-back action of œstrogen, so that the condition would seem to result from an excessive release of FSH.

The suggestion that electrolytic lesions in the anterior hypothalamus interfere with the regulation of FSH discharge receives support from recent work on the ferret. Donovan and van der Werff ten Bosch (1956*a*) have demonstrated that lesions placed just behind the optic chiasma in sexually quiescent animals in winter resulted in the onset of œstrus in about four weeks, long before blank operated control animals came into heat and at an abnormal time of the year. In these experiments it is clear that FSH is being released from the hypophysis in increased amount and it has been suggested that the lesion interferes with a mechanism inhibiting the secretion of FSH. Since the lesions were anterior to the median eminence the result cannot be attributed to the release of stored hormone following interference with the blood supply of the pars distalis, and an irritative effect of the lesion can perhaps be discounted because electrical stimulation of the anterior hypothalamus has so far failed to advance the onset of œstrus.

The existence of a mechanism inhibiting the release of gonadotrophic hormone has previously been postulated in explanation of the condition of pubertas præcox in children (Weinberger and Grant, 1941). However, few attempts have been made to test this concept experimentally. Clinically, the majority of tumours advancing puberty are located in the posterior hypothalamus and hence the action of lesions placed in this region has been studied, so far without any positive result (Bustamante, 1943; Gaupp, 1950). In view of the findings in the ferret the effect of lesions placed in the anterior hypothalamus of infantile rats was also investigated by Donovan and van der Werff ten Bosch (1956*b*). Small mid-line lesions were placed in the anterior hypothalamus of nine 14- or 15-day females and the animals examined regularly for vaginal opening. Two lesioned rats reached puberty at 30 days of age and four at 33 days. In one of eight sham-operated animals vaginal opening was noted on the 33rd day, but as all the rats were killed on the 20th day after operation observations on the other control animals could not be made. Study of a series of twenty-six normal rats revealed that only one animal reached puberty at 33 days, whilst the average age for puberty was approximately 41 days. Since this initial experiment lesions have been placed in a further series of rats and the findings in the first experiment have been confirmed. The vaginal smear has been followed in the second series and it is of interest that persistent œstrus has been found in some, but not all, of the lesioned rats in which puberty was advanced.

In considering the above experiments it seems possible that the hypothalamus is able to exert a restraining influence on the secretion of gonadotrophic hormones with perhaps a feed-back action of the gonadal hormones playing an important part in this mechanism. However, it would be unwise to suggest that the hypothalamic lesions producing constant œstrus in the rat, advancing the onset of œstrus in the ferret and causing precocious puberty in the rat, all interfere with a common mechanism. The fact that normal reproductive function and persistent œstrus can both be seen in rats in which puberty was hastened by hypothalamic damage points to caution in this respect.

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Dr. P. Kynaston Thomas and **Dr. David Ferriman:**

Constitutional Virilism

The investigations summarized in this paper began as an enquiry into the relationship between hirsuties and infertility in women. For a variety of reasons the assessment of infertility proved a matter of considerable difficulty and no definite conclusions could be reached. During the course of the investigation, however, a number of points emerged which were considered to be of interest.

At the outset of the investigation it was realized that there was no clear demarcation between hirsute and non-hirsute subjects. Growth of body hair varies widely both in men and women, and in fact appears to be a graded characteristic. It therefore became necessary to devise a system for grading the degree of hair growth. Of the various possible sites three were selected for study: the upper lip, the chin and lower abdomen. Five grades of growth were recognized at each site. Grade 0 represented the absence of hair. Minor degrees of hirsuties were common and were classified as Grades 1 and 2. More severe degrees, approximating to the popular conception of hirsuties, were less common, and were categorized as Grades 3 and 4.

An investigation into the variation in the incidence of hirsuties at these three sites and its variations with age was made on a series of approximately 600 female hospital patients between the ages of 15 and 84 seen in the general medical, general surgical and tuberculosis wards, one geriatric ward and one medical out-patient clinic at the North Middlesex Hospital. The series was unselected except in so far as diseases known to have effects on hair growth, such as myxœdema, were excluded. The results of this investigation are to be reported in full elsewhere (Thomas and Ferriman, 1957). Some features are of interest in the present connexion. A grading of 0 is clearly the most frequent finding in the pre-menopausal age groups, being found on three out of four occasions at any one site. Minor degrees of hirsuties are quite common. Major grades occur less frequently but still in significant numbers, being found at one or more sites in approximately 10–15% of individuals. The enquiry further revealed that these major forms of hirsuties first became apparent in the great majority of instances during adolescence. Striking changes take place in hair growth in the post-menopausal period of life. A marked increase occurs in the incidence of facial hirsuties, while hair virtually disappears from the lower abdomen.

The relationship between hirsuties and hair colour was also examined. Although the incidence of dark hair was slightly greater in hirsute than in non-hirsute subjects, the difference did not reach the level of statistical probability. The finding is in accordance with the results of previous workers.

Investigations were then carried out into the relationship between hirsuties and other masculine characteristics, and between hirsuties and oligomenorrhœa, and into the familial incidence of the condition. These investigations are being reported in full elsewhere (Ferriman *et al.*, 1957).

In order to assess whether hirsuties is accompanied by any other evidence of masculinization, measurements of shoulder and hip width and of urinary 17-ketosteroids excretion were obtained.

One of the most obvious skeletal differences between males and females is that shoulder width when expressed in terms of hip width is greater in the males. Measurements on approximately 40 subjects with a major degree of hirsuties at one or more sites demonstrated that the average bi-acromial width for these individuals was significantly greater than for a group of subjects with a zero or low hirsuties grading. Bi-iliac width did not differ between the two groups, and it is clear therefore that the observed difference in shoulder width did not depend upon differences in general body size or upon greater breadth of the trunk as a whole.

A similar comparison was made between the twenty-four-hour urinary 17-ketosteroid excretion in a group of approximately 60 patients with major grades of hirsuties and a group of subjects with zero or low hirsuties grading. The 17-ketosteroid excretion in the former group was found to be significantly greater.

The association generally believed to exist between hirsuties and oligomenorrhœa was explored during the course of the survey on the incidence of hirsuties, to which reference has already been made. Menstrual histories were taken from those patients between the ages of 15 and 44, together about 350 in number. The changes in hair distribution that are observed in later life precluded consideration of later decades. Employing strict criteria for the existence of oligomenorrhœa, a highly significant correlation between this type of menstrual disturbance and hirsuties was confirmed.

A somewhat limited enquiry was made into the incidence of hirsuties and oligomenorrhœa in the female relatives of hirsute individuals. As many mothers and sisters as possible of some 30 patients showing major grades of hirsuties were examined. Approximately 50% of both the mothers and sisters were found to have a major grade of hirsuties; this incidence,

considerably greater than that obtained in a control series, was statistically significant. Similarly there was an increased incidence of oligomenorrhœa in the relatives. These results thus confirmed the generally held belief that the condition is genetically determined.

It was concluded therefore that hirsute subjects show a distinct masculine tendency in two other directions, namely in having an increased shoulder width, and a raised urinary excretion of 17-ketosteroids. A high proportion have menstrual disturbances in the form of oligomenorrhœa. In view of the genetic background and the association of other masculine features with the hirsuties, the term constitutional virilism is suggested as an appropriate title for the syndrome.

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Dr. P. M. F. Bishop and **Mr. R. D. de Vere:**

The Stein-Leventhal Syndrome

In 1929 Stein performed his first wedge-resection for polycystic ovaries. In 1935 Stein and Leventhal described the classical features of the syndrome which consists of bilateral ovarian enlargement, amenorrhœa, hirsutism, obesity and vague and intermittent lower abdominal pain. In 1949, Stein *et al.* recorded 75 cases collected over a period of twenty years, since Stein performed his first operation. In only half this number of cases were there palpably enlarged ovaries. Klinefelter and Jones (1954) point out that this is largely due to the obesity and advocate gynæcography (induction of a pneumo-peritoneum followed by an X-ray examination), culdoscopy or even laparotomy.

Secondary amenorrhœa is the characteristic menstrual disorder; the condition does not develop before the menarche. Metropathia has occurred in some cases, as a manifestation of failure to ovulate. One case has been reported by Holmer (1950) in which regular, but non-ovulatory, menstrual cycles were present. Stokhuyzen (1950) recorded a case with regular, ovulatory cycles.

Hirsutism is found in only about 50% of the cases. It is occasionally associated with virilism.

In the majority of cases there is some degree of obesity and it is marked in about half the total number of cases.

Lower abdominal pain may be the presenting symptom in some cases.

On macroscopical examination the ovaries are obviously enlarged, firm, smooth, flattened, sclerotic and bluish-white—"oyster-ovaries".

On microscopical examination there are numerous microcystic follicles; the cortex is thickened and fibrotic and there are luteinized hyperplastic theca interna cells spreading into the theca externa and even appearing as isolated islands in the dense ovarian stroma.

The 17-ketosteroids were raised in only 5 out of 29 cases collected by Dorfman and Shipley (1956) and in 3 out of 5 cases studied by Bergman (1954).

Urinary gonadotrophins and œstrogens show normal values.

Fischer and Riley (1952) found a persistently raised urinary pregnanediol level in one case (though doubt has been cast on their method of estimation) and they postulate an excessive production of progesterone by the thecal cells leading to a suppression of production and release of luteinizing hormone which would hinder ovulation, though there might be a continuous production of follicle stimulating hormone, which might account for the microcystic follicles.

It may, however, be significant that the ovarian lesion is bilateral and Culiner and Shipel (1949) postulate that there is excessive production of luteinizing hormone to account for the ovarian hyperthecosis. In one of their cases ovarian enlargement developed only after administration of chorionic gonadotrophin for some menstrual irregularity.

Ingersoll and McDermott (1950) emphasize the "collagenous infiltration of the ovarian capsule" and regard this as a mechanical barrier to ovulation. This might explain the beneficial effects of wedge resection. It has even been found that bisecting the ovaries and sewing the two portions back to back gives equally satisfactory results.

Whatever the pathogenesis of the syndrome may be the results of wedge resection are most dramatic. Stein *et al.* re-established normal, ovulatory menstrual cycles in 67 of their 75 cases and conception followed within a few months in 26 of their 40 patients complaining of infertility.

There is, however, unfortunately, seldom any regression of hirsutism.

The object in presenting the following two cases of the Stein-Leventhal syndrome is to show that this syndrome may exist in the absence of many of the signs and symptoms originally described, and in the presence of other features, which by the same token would seem

to exclude it. The already well-recognized success of wedge resection of the ovaries in these cases is also clearly demonstrated.

Case I.—Mrs. W., aged 21. Married. Nulliparous.

This patient was referred to the Endocrine Clinic at Chelsea Hospital for Women from a Maternity Hospital which she had attended under the impression that she was pregnant. Her complaints were: (1) Amenorrhœa for one year, her menstrual periods having been regular and normal before this. (2) Increasing hirsuties for the past four months. (3) Rapid increase in weight over the past seven months. (4) Inability to become pregnant during the two years of her marriage.

Examination showed that she was a markedly obese young woman of normal stature with dark hair. She had pronounced "side-whiskers" extending to the angles of the jaw, and an obvious moustache which she made no attempt to disguise. She had marked hirsuties of the breasts, abdomen and thighs and the pubic hair was of the so-called "male" type. There were no other masculinizing signs. Owing to her obesity, pelvic examination was difficult, but the uterus appeared to be normal in size. What was assumed to be the enlarged left ovary could be felt but the right ovary was not palpable.

B.P.: 120/80. *Urine:* No sugar. 17-*ketosteroids:* 12·6 mg./twenty-four hours.

Examination under anæsthesia showed both ovaries to be symmetrically enlarged and this was confirmed at *laparotomy* when the typical sclerocystic ovaries were found. They measured approximately 5 × 3 × 2 cm. each. Five-eighths of each ovary was removed by wedge resection and the ovaries were reconstituted with an atraumatic suture.

Section of the ovarian tissue showed all the characteristics of the Stein-Leventhal ovary.

Regular ovulatory menstrual cycles were resumed two months after the operation, and the patient has since delivered a normal child at term. Her weight and the extent of the hirsuties are unchanged.

Case II.—Miss E., aged 33. Unmarried. Nulliparous. Her complaints were: (1) Hirsuties for fifteen years becoming progressively worse. (2) Baldness for the same time, also getting worse, and for which she wore a wig. (3) Irregular, infrequent and prolonged menstrual periods for five years, these having been normal and regular before this.

Examination showed that she was a young woman of normal stature and contour. She was not obese. There was generalized facial hirsuties effectively disguised by electrolysis, plucking and liquid make-up. She wore a wig to conceal marked baldness of the tonsure type and some recession at the temples. There was moderate hirsuties of the breasts, abdomen ("male type" pubic hair) and legs.

Both ovaries were palpably enlarged on pelvic examination.

B.P.: 130/75. *Urine:* No sugar. 17-*ketosteroids:* 9·2 mg./twenty-four hours.

On examination under anæsthesia both ovaries were found to be symmetrically enlarged. *Curettage* produced abundant endometrium which on section showed cystic glandular hyperplasia.

At laparotomy typical Stein-Leventhal ovaries were found, each measuring approximately 6 × 4 × 2 cm. Wedge resection was performed as in Case I.

Since operation (twenty months) she has had normal, regular menstrual periods. The extent of her hirsuties has not progressed, neither has it regressed. Her baldness has improved markedly, and she has been able to discard her wig, but this may be due to the application of hydrocortisone ointment during the past year. As the result her morale has improved dramatically, and from being decidedly aggressive she is now co-operative.

The atypical features in this case (Case II) are the presence of a metropathic type of menstrual history as opposed to amenorrhœa, the absence of obesity, and the presence of baldness. As these cases are not invariably accompanied by hirsuties it may be justifiable to assume that some cases of metropathia (cystic glandular hyperplasia of the endometrium) have sclerocystic ovaries and would perhaps benefit by wedge resection of the ovaries provided the typical appearance of the ovaries was found on laparotomy.

As has been said, cases of the Stein-Leventhal syndrome vary widely in their symptomatology. There may or may not be hirsuties; obesity is not invariably present and as in Case II there may not even be amenorrhœa (Greenblatt, Holmer, Stokhuysen, Menher *et al.*). The diagnosis finally rests, therefore, on the demonstration of the characteristic condition of the ovaries.

Ovarian enlargement frequently escapes the most careful clinical examination particularly in the virgin and in the presence of obesity. In the United States culdoscopy is widely practised and would seem to be the ideal method of demonstrating minor degrees of ovarian enlargement. It is not without its difficulties, even in the hands of the expert, and the authors, in common with most gynæcologists in this country, have little experience in its use. It would be extremely valuable in a doubtful case where examination under anæsthesia had failed to demonstrate enlarged ovaries.

Similarly objections apply to the use of X-rays following the induction of a pneumoperitoneum ("pneumo-Roentgenology"), and although some very impressive X-ray photographs have been reproduced in the American literature, we have had no success with this method. Further objections are that it demonstrates only the size of the ovaries, not their consistency, and then only in relation to the size of the uterus. Also, the wisdom of irradiating the ovaries of young women of reproductive age has recently been questioned.

In the authors' view examination under anæsthesia is the most satisfactory method and we have found that with the use of relaxant drugs we have been able to feel the ovaries, enlarged or not, in all cases in question. A more difficult question to decide is whether or not the ovaries are enlarged, and in our experience laparotomy has shown them to be larger than was anticipated. We have yet to meet the case where both ovaries were impalpable under anæsthesia.

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Dr. Raymond Greene protested against too wide an application of the term Stein-Leventhal syndrome and feared that we were in danger of considering that all women who were fat or hairy or suffered from any kind of menstrual disturbance were suffering from incomplete forms of the syndrome. He drew attention to the fact that although wedge resection of the ovaries corrects the menstrual abnormality and may even make pregnancy possible, it rarely, and in his experience never, helps the obesity or hypertrichosis. He quoted the case of a previously pretty Hungarian girl with the complete syndrome who came under his care after an attempt at suicide. Wedge resection had the usual result and her depression deepened. Strict dieting produced only a very slow reduction of her weight, originally 13 st. 4 lb. The output of 17-ketosteroids was normal (7·85 mg. in twenty-four hours) and was not raised by treatment with chorionic gonadotrophin. It was decided that her depression warranted extreme measures and a subtotal adrenalectomy was performed. The adrenals were histologically normal, though one was slightly enlarged (weights of excised portions 8·5 and 13·6 grams (total)). No dramatic effect followed, but a steady improvement has occurred during the two years which have elapsed. She has shaved at gradually increasing intervals, her weight without dieting has dropped to 10 st. 12 lb., and her menstruation has remained normal.

[*February* 27, 1957]

THIS Meeting of the Section was devoted to discussion of the subject matter of the recent Conference of the Ciba Foundation on **Hormones in Blood.** The speakers were Dr. M. SONNENBERG, Dr. E. B. ASTWOOD, Dr. L. T. SAMUELS and Professor C. J. O. R. MORRIS.

[*March* 20, 1957]

A JOINT MEETING was held between the Section of Endocrinology and the Society for Endocrinology. The meeting took the form of a Symposium on "Investigations on Subjects Relating to Obesity and Diabetes". An Introduction was given by Sir Charles Dodds. The titles of the papers presented were as follows:

The Effect of Age on the Somatic and Visceral Response to Over-nutrition in the Rat.—Dr. G. C. KENNEDY.

Metabolic Changes on Reducing Diets.—Dr. J. A. STRONG and Dr. R. PASSMORE.

Obesity, Parity and Diabetes.—Dr. D. PYKE.

Observations on Human Reproduction and Body Weight.—Dr. T. MCKEOWN and Dr. R. G. RECORD.

The Hypothalamus and Carbohydrate Regulation.—Dr. A. PATON.

Pituitary Growth Hormone and Blood Insulin.—Dr. P. J. RANDLE.

Insulin Activity and Antagonism in the Plasma of Diabetic Patients and Animals.—Dr. J. VALLANCE-OWEN.

The Antidiabetic Sulphonamides.—Dr. D. M. DUNLOP and Dr. L. J. P. DUNCAN.

Summing up by Dr. T. RUSSELL FRASER.

The meeting will be fully reported in the *Journal of Endocrinology*.

JOINT MEETING No. 3

Section of Pathology with Section of Physical Medicine

Chairman—Professor JOHN W. S. BLACKLOCK, M.D.
(President of the Section of Pathology.)

[*February* 19, 1957]

DISCUSSION ON RHEUMATOID DISEASE

Dr. W. S. Tegner (The London Hospital): *The Clinical Aspect*

The clinician who is interested in rheumatoid arthritis is more likely to see and discuss his patients with the clinical pathologist than with the morbid anatomist. This is due to more than one factor: the pathology of rheumatoid arthritis is not established and exact; it is also true that our patients are not suffering from a killing disease and do not come to the post-mortem table because of rheumatoid arthritis. For in this antibiotic age it is no longer possible for us to say quite so readily that our patients die of intercurrent infection. I find that my poor old cripples now get over their bronchopneumonia and continue to exist for longer periods. If we prolong the lives of our rheumatoid arthritics we must not at the same time prolong their sufferings, otherwise we increase the burden on all those who care for the crippled and incurable.

The rheumatoid arthritic who reaches the post-mortem table usually comes from a hospital bed to which she has been admitted for some other condition. Usually the rheumatoid arthritic dies at home. But if she is afflicted at the same time with some other interesting condition, the hospital will take her in when she is seriously ill. This has caused a difference in the opinion on the incidence of such a condition as amyloidosis in rheumatoid arthritis. I have looked for amyloidosis among my rheumatoid arthritics—and I have more than a thousand on my books—but I have found only one. On the other hand, the morbid anatomists at The London Hospital find an incidence as high as 25% among the rheumatoid arthritics who come into their hands. When the clinician finds he has a rheumatoid arthritic displaying some particularly interesting feature such as amyloid disease he makes sure that that patient dies in hospital. In this way the rarer and more interesting conditions associated with rheumatoid arthritis get into the hands of the morbid anatomists in far higher proportion than they are found in a living series.

Biopsy in rheumatoid arthritis.—I want to take only a few rather isolated instances, which I have met more than once. Epitrochlear adenitis is commonly seen when the arthritis involves the wrists and fingers. There is nothing unusual in such adenitis, yet the Wassermann reaction is inevitably done and has proved negative, and so a biopsy is ordered.

Another unusual point of contact between the morbid anatomist and the clinician dealing with arthritis has been in Hodgkin's disease. One patient was found to have a diffuse enlargement of the lymph glands and some other curious lumps. He was also febrile, and had a palpable liver and spleen. A diagnosis of Hodgkin's disease was made, and radiotherapy was started before a lump from the occipital region was sent for examination. The pathologist reported this to be a typical rheumatoid nodule, and naïvely enquired " did the patient exhibit any arthritis?" In this case the pathologist made the diagnosis, and it was not until he had done so that I was called in to confirm it. Last month I had a patient referred to me with the story that a mass of glands, thought to be enlarged through Hodgkin's disease, had been removed five years ago from his groin, after which he was treated by radiotherapy and got well. After three years he was not so well, and complained of general aches and pains. Finally it was decided he was suffering from rheumatoid arthritis, and he was put on cortisone, which did him neither harm nor good. He was referred to me on cortisone as suffering from rheumatoid arthritis. I could find no evidence of arthropathy and on looking at the original slide, the patient proved to be suffering from Hodgkin's disease. Though such instances of rheumatoid arthritis presenting as a differential diagnosis of Hodgkin's disease must be exceedingly rare, yet I have met such a situation twice in the last ten years.

The joints in rheumatoid arthritis.—Clinicians sometimes overstress the joint pathology and forget that rheumatoid arthritis is a general systemic disease with many extra-articular manifestations. The deformity pattern adopted by a joint depends not on the disease but on the anatomy of the affected joint; thus, I have seen extreme ulnar deviation of the fingers in classical gouty arthritis. Even in rheumatoid arthritis of the fingers ulnar deviation only occurs in about 25% of patients.

Rheumatoid arthritis presenting as a mono-articular arthropathy.—I see such patients at regular intervals in consultation with orthopædic surgeons. Usually they have been diagnosed on clinical and radiological grounds as suffering from tuberculous arthritis and surgical debridement has been advised. At operation the surgeon finds that the appearances are not those of tuberculous arthritis and sends synovial membrane for biopsy, after which his opinion that the joint is not after all tuberculous is confirmed. The patient usually develops further rheumatoid joints after this. I would have thought that a simple aspiration of joint fluid before operation would be advisable, but I suppose the vast majority of tuberculous joints are correctly diagnosed and such a pre-operative diagnostic procedure is regarded as unnecessary. It is of interest that in these days, when joint tuberculosis can be treated so admirably by a combination of surgery, chemotherapy and antibiotics, it is of much better prognosis to have tuberculous rather than rheumatoid arthritis.

Dr. Bruce Cruickshank (Pathology Department, Glasgow Royal Infirmary): *Rheumatoid Arthritis and Rheumatoid Disease*

The term "rheumatoid arthritis" implies a disease entity involving the joints, in which the changes are rheumatic-like. The clinical features in patients with "rheumatoid arthritis" are similar to those of other rheumatic diseases. Indeed, the condition is one of the most important within that group. Are these clinical features associated with specific pathological changes? The term "rheumatoid disease" is being used with increasing frequency: implying a condition not confined to the joints. Is this a clinical syndrome or a pathological entity?

Synovial Lesions

Some authors have stated that the lesions in the synovial tissue in "rheumatoid arthritis" are specific. Allison and Ghormley (1931) laid great stress on the presence of lymphocytic foci and regarded them as specific to the disease. Key (1934) described lesions in traumatic synovitis which were basically the same as those in "rheumatoid arthritis" and most other writers during that decade regarded the lymphocytic foci as non-specific. The two most recent studies of large collections of material have led their authors to opposing conclusions. Bennett (1941) found lymphocytic foci in conditions other than "rheumatoid arthritis" and concluded that the lesions of "rheumatoid arthritis" were not specific. On the contrary, Collins (1949) regarded certain changes as diagnostic of "rheumatoid arthritis", provided that the specific features of other diseases, such as tuberculosis, were absent.

The data presented here are condensed from a study of all specimens of synovial tissue from joints, bursæ and tendon sheaths received in the Departments of Pathology, University and Royal Infirmary, Edinburgh, during the period 1935–1951 and of additional material from examples of rheumatic diseases collected by the author during the period 1948–1951 (Cruickshank, 1952*a*). Table I shows the incidence, in the various diseases studied, of the complete combination of changes described by Collins, and of necrosis, which is another common feature of synovial tissue in "rheumatoid arthritis." Those examples of "rheumatoid arthritis" and ankylosing spondylitis in which old-standing fibrosis was the predominant feature (30 and 7 joints respectively) are excluded from Table I. The complete combination of changes occurs in several conditions other than "rheumatoid arthritis", some of which, such as tears of menisci, are unlikely to be confused with "rheumatoid arthritis", whereas others, such as non-specific monarticular arthritis or tenosynovitis, may be the presenting clinical feature of "rheumatoid arthritis". Indeed, a few of the examples of non-specific arthritis and tenosynovitis may have been atypical or early cases of "rheumatoid arthritis", for an adequate follow-up was not always possible; but "rheumatoid arthritis" could be excluded in most of them. In such cases histological examination cannot clinch the diagnosis. A diagnostic appearance was seen only in the occasional instance where necrosis constituted part of granulomatous foci such as occur in the subcutaneous nodule in "rheumatoid arthritis". A closer resemblance to this type of reaction ("the rheumatoid granuloma") has been reported in early synovial lesions (Kulka *et al.*, 1955) than in most of the established lesions studied here. In the absence of such foci the pathologist cannot say more than that the appearances are compatible with the diagnosis of arthritis of the rheumatoid type; final assessment of the patient must be made by the clinician.

TABLE I.—INCIDENCE IN SYNOVIAL TISSUE OF LESIONS "CHARACTERISTIC" OF "RHEUMATOID ARTHRITIS" IN VARIOUS DISEASES

Diagnosis	Number of specimens examined	Lesions of "rheumatoid arthritis" present	Necrosis present
"Rheumatoid arthritis"—joint	54	24	24
" " —bursa	8	—	6
" " —tendon sheath ...	4	3	1
Ankylosing spondylitis	4	2	3
Degenerative joint disease	31	1	—
Gout	5	—	—
Rheumatic fever	14	—	9
Systemic lupus erythematosus—joint ...	8	—	—
" " " —tendon sheath ...	2	—	1
Polyarteritis nodosa	5	—	—
Non-specific synovitis —joint	41	9	2
" " —bursa	114	3	1
" " —tendon sheath ...	75	13	12
Lesions of menisci—tears	28	4	3
" " " —cysts	19	—	—
Tuberculosis—joint	35	2*	35†
" —bursa	6	—	6†
" —tendon sheath	27	2*	27†
Loose bodies, septic arthritis, &c.	23	—	—
	503	63	130

* Tubercle follicles also present.
† Necrosis of caseous type.

VISCERAL LESIONS

The involvement of tissues other than the joints and subcutaneous tissue in patients with "rheumatoid arthritis" has been known for many years though most papers have appeared in the last fifteen years. Almost any organ or tissue may be involved by non-specific lesions, by "rheumatoid granulomata" or both. Such lesions have been encountered in hospitalized patients, who represent a selected group of sufferers from the disease. Indeed, many reports have been limited to the description of lesions found in one or two such patients. These studies give no indication of the incidence of visceral lesions in the disease as a whole, as distinct from particular groups of patients, selected for a variety of reasons. Some of the systemic lesions are associated with clinical features, such as splenomegaly, episcleritis, &c., but others are detected only at autopsy, so that the true incidence of such changes can be obtained only from clinical and pathological studies of large numbers of patients. Full details of the whole of the clinical course of the disease are not always available, which makes it difficult to assess the significance of all lesions found at autopsy.

A series of 100 autopsies on patients who had suffered from the disease provides the material for the present review of visceral lesions. 49 of these patients were admitted to hospital for treatment of "rheumatoid arthritis" or its complications, 51 for the treatment of intercurrent disease. Table II shows the incidence in various tissues and organs of lesions

TABLE II.—INCIDENCE OF SYSTEMIC LESIONS IN 100 EXAMPLES OF "RHEUMATOID ARTHRITIS"

Heart:			
endocarditis alone	4		
myocarditis alone	3		
pericarditis alone	3	18	
arteritis alone	8		
endocarditis and amyloidosis ...	1		
myocarditis and arteritis... ...	1	2	30
pericarditis and arteritis	1		
endo-, myo- and pericarditis ...	3		
endo- and pericarditis and arteritis	4	9	
myo- and pericarditis and arteritis	2		
Arteritis (in organs other than the heart)		13	
Pleuræ			42
Spleen			12
Lymph nodes			11
Muscle (in biopsy and autopsy series of 93)			39
Nerve (in 20 autopsies)			14
Subcutaneous tissue			8
Pharynx ("rheumatoid granuloma") ...			1
Pituitary (degeneration of basophils) ...			1
Kidney (glomerulitis)			1
Salivary or lacrimal glands			2
Amyloidosis			7

which cannot be accounted for by intercurrent disease found at autopsy or mentioned in the clinical notes. Such lesions were found in 73 patients. Are these all systemic lesions of "rheumatoid arthritis"? "Rheumatoid granulomata" were found in the heart in 6 patients, in the spleen in a seventh and in the pharynx in an eighth. These lesions are frequently

regarded as specific, but similar nodules have been observed occasionally in patients who have not developed other stigmata of "rheumatoid arthritis" (Findlay, 1931; Klinge, 1933; Bergstrand, 1944; Cruickshank, 1952*a*). The lesions in the remaining 65 patients were certainly non-specific. It is not possible to discuss all the histological details in the present communication; the nature and interpretation of some of them have been discussed previously by Cruickshank (1952*a*, 1952*b*, 1954, 1957) and Sinclair and Cruickshank (1956). Thus it has been shown that there is good evidence for regarding much of the endocarditis, active or apparently healed, as being part of the "rheumatoid disease" rather than of an independent attack of rheumatic heart disease (Cruickshank, 1952*a*; Sinclair and Cruickshank, 1956). Evidence of the latter condition was seen in 4 patients; in another 2 patients healed valvular disease was present but microscopic sections were not studied. Most of the evidence that the cardiac lesions are rheumatoid, rather than rheumatic, is derived from histological studies. It is much more difficult to prove the relationship of the lesions in the myocardium and pericardium to the rheumatoid process; they frequently accompanied endocardial changes and were the sole cardiac lesion in only 6 cases, in 2 of which there was ample other evidence of systemic involvement. Most of the arterial lesions which occurred in these patients have been described and discussed by Cruickshank (1954). No "rheumatoid granulomata" were seen in the pleura. Aronoff *et al.* (1955) has argued that it is intellectually unsatisfactory to ascribe lesions for which there is no other obvious cause to the rheumatoid process. This may be so, but it is not surprising to find a high incidence of pleural involvement in this disease which may affect so many parts of the connective tissues. Indeed Aronoff *et al.* found pleural adhesions in 27 out of 42 autopsies in "rheumatoid disease" and in only 12 out of 42 controls. Baggenstoss and Rosenberg (1944) had previously found pleurisy in 22 out of 30 autopsies in "rheumatoid arthritis." Emerson (1956) has recently described pleural effusions in 6 patients with "rheumatoid arthritis" in whom no other cause could be demonstrated. It is unlikely that 42 out of 100 represents the true incidence of pleural involvement in "rheumatoid disease", for Sinclair and Cruickshank (1956) found pleural adhesions without apparent cause in 20 out of 90 controls. In the series now under review, the pleural adhesions were not associated with other systemic lesions known to occur in "rheumatoid arthritis" in 18 of the patients, so that a figure between 20 and 40% probably represents the occurrence of pleurisy as part of "rheumatoid disease". Involvement of the spleen and lymph nodes is generally accepted as a feature of "rheumatoid arthritis"; the lesions encountered in the lymph nodes in the present series have been described by Cruickshank (1957). Lymphorrhages in muscle and nerve are included in Table II for, although not specific (Clawson *et al.*, 1947; Sokoloff *et al.*, 1950), they occur more frequently, and are more numerous in "rheumatoid arthritis" than in other conditions (Cruickshank, 1952*b*) and are therefore probably part of the systemic disease. The low incidence of degeneration of pituitary basophils (Pearse, 1950, 1956) was due to the infrequency with which this gland was examined in the earlier autopsies and to the inadequate freshness of many of the later autopsies. The glomerulitis was similar to that encountered by Baggenstoss and Rosenberg (1943). The interpretation of amyloidosis as a systemic manifestation of "rheumatoid disease" was discussed by Sinclair and Cruickshank (1956). The relationship of these various visceral lesions to the activity of the joint lesions at the time of death is shown in Table III.

TABLE III.—INCIDENCE OF VISCERAL LESIONS IN RELATION TO ACTIVITY OF ARTHRITIS AT AUTOPSY

	Joint lesions active	Joint lesions inactive	Total
One organ or tissue involved	11	23	34
Two organs or tissues involved ...	7	13	20
Three or more organs or tissues involved	12	7	19
Visceral lesions active	20	13	33
Visceral lesions inactive	10	30	40
Total number of cases	30	43	73

It is important to note that widespread and active visceral lesions may occur in patients whose arthritis is no longer active. When the patients in whom myocarditis, pericarditis or pleurisy were the only visceral lesions are deducted from the total, there remain 52 patients with visceral lesions attributable to the rheumatoid process.

Considerable interest has been stimulated recently by the description of certain lung lesions in "rheumatoid arthritis". "Rheumatoid granulomata" have been described by Ravel *et al.* (1948), and several other authors. In view of the pleomorphic nature of the lesions of pulmonary tuberculosis, it is essential that this condition be excluded in all suspected examples of "rheumatoid granulomata" of the lung. Investigation of these lesions should include amino-acid analysis (Consden and Glynn, 1955); failure to demon-

strain tubercle bacilli by the Ziehl-Neelsen stain cannot be regarded as excluding tuberculosis, particularly when the granulomata are confined to the lungs and hilar lymph nodes (Skogrand, 1956) or are atypical (Christie, 1954, Case 1). Modified "rheumatoid granulomata" have been described in the lungs of patients with pneumoconiosis by Gough *et al.* (1955). Interstitial pneumonia has been observed by Ellman and Ball (1948) and several other authors. The relationship of interstitial pneumonia and diffuse interstitial pulmonary fibrosis to "rheumatoid disease" has been reviewed recently (Rubin, 1955). None of the several authors who have described this type of lesion has regarded it as specific. Recently Price and Skelton (1956) have described focal arteritis and bronchiolitis in one patient. Neither nodular lesions, nor the changes described by Price and Skelton were seen in this series. However, there were six examples of interstitial pneumonia. The lesions were all chronic and were accompanied by diffuse or focal fibrosis. Associated bronchiectasis was seen twice, causing honeycomb lungs in one patient. These lung lesions have not yet been studied in detail. The incidence of interstitial fibrosis in a series of 6,000 unselected autopsies reviewed by Mallory (1948) was 16. It thus seems likely that the association of interstitial pneumonia and fibrosis with "rheumatoid disease" is more than coincidental.

It is appreciated that many patients suffering from "rheumatoid arthritis" are not admitted to hospital and that few of those who die are examined by a pathologist. Nevertheless, this series includes a considerable number of patients whose arthritis was inactive on admission to hospital and remained so until death, which was due to an unrelated disease. Active visceral lesions were found in some of these patients. The clinical and pathological features in 16 of the patients with widespread visceral involvement has been discussed by Sinclair and Cruickshank (1956) who found that the visceral lesions, particularly those in the heart, were the main cause of death in 8 patients and a major contributing factor in another 7 patients. Surely it is more correct to regard these patients as suffering from "rheumatoid disease" (Ellman and Ball, 1948), than "rheumatoid arthritis", however convenient the latter may be as a clinical diagnosis. It must be emphasized that the term "rheumatoid disease" as used by Ellman and Ball and most subsequent authors is applied to patients in whom joint lesions were a cardinal feature at some stage in the disease. The patients reviewed here all presented with arthritis of the rheumatoid type. "Rheumatoid disease" in this sense is not to be confused with the "anarthritic rheumatoid disease" of Bagratuni (1956), the histological features of which have not yet been described. Although few, if any, of the systemic lesions are truly specific, the combination of joint and visceral lesions of "rheumatoid disease" give an overall pathological picture which has not been described in any other condition. "Rheumatoid disease" must, therefore, be considered a pathological entity rather than merely a clinical syndrome.

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Dr. A. T. Richardson (Royal Free Hospital): *Routine Clinical Pathology in Rheumatoid Arthritis*

Rheumatoid arthritis, although usually defined as a non-suppurative polyarthritis of unknown ætiology, is now generally regarded as a systemic disease with widespread connective tissue involvement. Thus, its diagnosis is based not only on the character and distribution of the arthritis but also upon the co-existence of a constitutional disturbance, and on the results of one or more of a bewildering number of serological reactions. In this paper I would like to review the value of some of the laboratory investigations used routinely in the diagnosis and management of this disease. It is based on clinical experience with 332 cases referred to the Department of Physical Medicine and Rheumatology, Royal Free Hospital, during 1954 and 1955.

Without doubt the erythrocyte sedimentation rate (E.S.R.) is the most widely used investigation in the diagnosis of rheumatoid arthritis, it being generally accepted that it is raised during the active phase of the disease. Fig. 1 shows the first hour E.S.R.s (Westergren) in

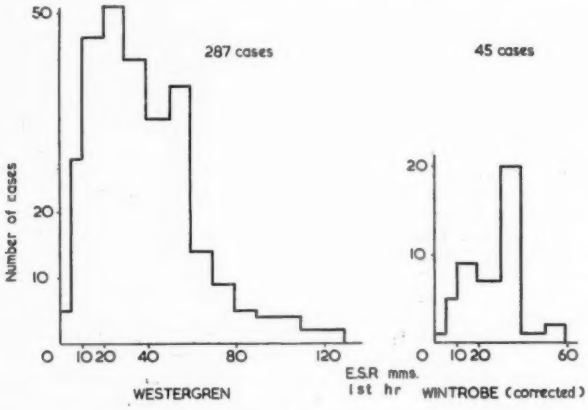


FIG. 1.—Erythrocyte sedimentation rates in rheumatoid arthritis at first attendance.

287 consecutive patients and first hour E.S.R.s (Wintrobe corrected) in 45 others at their first attendance. The cases with normal sedimentation rates (11·5% under 10 mm. in first hour in the Westergren series) were by no means entirely those with burnt-out disease attending for correction of residual deformities or for treatment of superadded degenerative joint changes, for 14 of these 33 had signs of active disease in non-weight-bearing joints and showed within one year of their attendance a raised E.S.R. of more than 35 mm. and progression of the disease. A further 2 cases had active and progressive disease for over two years with a persistently normal E.S.R.

Second only to the use of the sedimentation rate in this disease is the estimation of the hæmoglobin level. Fig. 2 shows the range of values in a series of 294 consecutive patients at first attendance, 75% showing values of over 80%.

However, the use of E.S.R. and hæmoglobin estimations in the diagnosis of rheumatoid arthritis is of greatest value at the stage of a prodromal constitutional disturbance, e.g., anorexia, excessive fatigue or transient muscle pains and stiffness, &c. Similarly it is of great value in the early diagnosis of the surprising number of cases labelled as metatarsalgia, capsulitis of the shoulder, tenosynovitis, bursitis, painful heel, &c., who subsequently develop a polyarthritis. In this connexion it is interesting that a large number of a series of patients with unexplained persistently raised E.S.R.s, followed by Ansell and Bywaters (1957) subsequently developed rheumatoid arthritis.

It is for such cases and indeed to define rheumatoid arthritis and its variants more accurately that a reliable and specific laboratory test is required. Of all the serological reactions investigated so far, the sheep cell agglutination test (D.A.T.) has proved to be the most specific. The technique that has been used is the modification described by Ziff and his colleagues (1954), the so-called euglobulin agglutination test. They claimed 92% of positive results in 82 cases of rheumatoid arthritis as opposed to 78% using whole serum and a reduction in the number of false positives. In contrast, Bernstock, Bedson and Glynn (1956) reported disappointing results with this technique although they confirmed the low

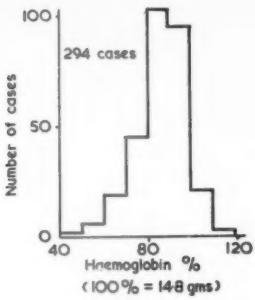


FIG. 2. — Hæmoglobin levels in rheumatoid arthritis at first attendance.

rate (2%) of false positives. The first 300 patients tested by Dr. E. Hess, who has carried out this work in my Department, included 130 with rheumatoid arthritis of which 110, or 85% gave a positive result at titre of 1/64 (Table I), of these, 22 had a history of under six months.

TABLE I.—RESULTS OF EUGLOBULIN ROSE'S TEST

Disease	Total cases	Number positive
Rheumatoid arthritis	130	110
Rheumatoid variants	3	3
Rheumatoid arthritis with psoriasis ...	5	—
Dermatomyositis, neuromyositis and polymyositis	5	2
Systemic lupus erythematosus	9	6
Osteoarthritis	44	1
Gout	6	—
"Menopausal" arthritis	15	1
Specific arthritides	4	—
Rheumatic fever	3	—
Ankylosing spondylitis	12	—
Normal controls and other diseases ...	64	—

The 20 negative cases included 6 with titres of 1/32. Of the remaining 14 rheumatoids with negative results, 4 had histories of under six months and 3 had inactive disease. 9 cases of rheumatoid arthritis with a positive euglobulin test but an initially normal E.S.R. have occurred and we have one case of tenosynovitis with a normal E.S.R. and positive euglobulin test who subsequently developed rheumatoid arthritis. Positive results have also been obtained in systemic lupus erythematosus and some members of the polymyositis syndrome. In the other arthritides, such rheumatoid variants as Reiter's, Sjögren's and Still's disease have shown positive results. In contrast, psoriatic arthritis has given consistently negative results and indeed a negative Rose's test has become accepted as one of the criteria for this diagnosis (Wright, 1956). Of considerable interest also is the fact that the so-called mixed or menopausal arthritis (a distinct clinical entity) rarely shows a positive Rose's test. Similarly, patients with ankylosing spondylitis give a negative Rose's test as do an array of other diseases.

Serological investigations, no matter how complete, do not entirely eliminate the need for joint biopsy and for examination of the synovial fluid for organisms; in particular it is in cases with an insidious onset of pain and swelling of a single large joint that such investigations are required. In my series no less than 36% had a large joint onset, it occurring most commonly in men and sometimes in a single joint whose fluid could not be obtained, an occurrence peculiarly suggestive of tuberculous infection and needing biopsy. In fact, no case of a tuberculous joint occurred during the period surveyed in this review; the only specific types found were 2 following Neisserian infection, 1 following meningococcal infection and 1 following staphylococcal infection in a patient on cortisone.

The indication for biopsy in the diagnosis of rheumatoid arthritis is, however, not confined to joints; in particular it has a place in the differential diagnosis of tenosynovitis. Thus while it is well-known that nodular tendonitis and tenosynovitis may co-exist with rheumatoid polyarthritis, that these lesions may precede joint involvement is not so widely appreciated. In my series the onset was in the tendon sheaths in 7, and in 3 cases, reported elsewhere by Jacobs, Hess and Beswick (1957), tenosynovitis, whose rheumatoid origin was indicated by biopsy, preceded the polyarthritis respectively by four, fourteen and eighteen months, 2

cases having a normal E.S.R. during that time although one had a positive differential agglutination test.

The prognosis of rheumatoid arthritis is, of course, notoriously unpredictable both clinically and in terms of pathological findings. Most of the work on this has been done on patients admitted to hospital, the most recent series being that of Duthie and his colleagues (1955) whose conclusion was that a high E.S.R. in the early stages carries a relatively good prognosis, but in the late stages a bad one. There are, however, many contradictions to this rule.

In an endeavour to illustrate the place of the E.S.R. in prognosis I have taken from the records 39 of the functionally most mildly affected cases and 33 very severely affected ones, in fact rheumatoid cripples, as judged at three years from their first attendance. The state of their E.S.R.s and hæmoglobins at first attendance compared with the total series showed no significant deviation at the ·05 level (Table II). The most significant finding was a low

TABLE II.—RESULTS AT FIRST ATTENDANCE

	E.S.R.s mm. First hour (Westergren)		Hæmoglobin %	
	Mean and S.E. of mean		Mean and S.E. of mean	
Total Patients ...	(287)	36·5 ± 1·4	(294)	85·8 ± 0·7
Mildly affected ...	(39)	44·0 ± 4·5	(39)	87·8 ± 2·2
Severely affected ...	(33)	42·1 ± 4·6	(33)	81·8 ± 2·4
Steroids used ...	(28)	38·8 ± 5·5	(22)	86·7 ± 3·3

hæmoglobin in the severely affected and a high E.S.R. in the mildly affected. As another index I have taken 28 cases who ultimately required long-term steroid therapy. As, in general, the indication for this was progressive systemic illness in spite of prolonged hospitalization, it is perhaps more an index of systemic disease than are functional studies. However, again the level of the E.S.R.s and hæmoglobins at first attendance compared with all groups showed no significant variation.

Study of the trends in these E.S.R.s and hæmoglobins over three years again showed no marked changes although 4 cases who showed a very high initial E.S.R. (80–100 mm. first hour) which dropped after hospital admission retained good function for three years. These are, of course, examples of patients whose rheumatoid arthritis was of explosive onset, but in whom hospitalization brought about a rapid remission and who, therefore, on clinical grounds alone would be regarded as having a relatively good prognosis. The most significant difference between those severely and those mildly affected was the duration of the illness before they first attended, the mean of the former being 8·3 years and of the latter, 4·1 years.

Any discussion on the place of routine clinical pathology in the diagnosis and prognosis of rheumatoid arthritis would be incomplete without some reference to the occurrence of widespread extra-articular connective tissue changes in this disease. The common occurrence of these has encouraged some to recommend the use of the term "rheumatoid disease" in place of "rheumatoid arthritis". Certainly in clinical usage "rheumatoid disease" or "soft tissue rheumatoid" is being increasingly applied where it is not the polyarthritis but the co-existing vascular, muscle or other soft tissue lesions or even the general constitutional disturbance which dominate the clinical picture but where pathognomonic clinical signs and the absence of L.E. cells, &c., do not indicate an alternative diagnosis, although the progress of the patient may well do so. Diagnosis in these circumstances is, however, difficult, for while members of their so-called connective tissue group of diseases possess a common pattern of pathological change, they exhibit a wide variety of clinical manifestations very few of which are pathognomonic and many of which are common to all.

My experience is based on 8 cases additional to the series of 332 cases who presented as polyarthritis but whose subsequent progress demanded a revision of the initial diagnoses: 7 into systemic lupus erythematosus and 1 into progressive systemic sclerosis. In 5 of these cases the true diagnosis was reached on clinical grounds alone, but in 2 the behaviour of the E.S.R. was largely responsible.

The patient with systemic sclerosis presented with a polyarthritis which was accompanied by severe Raynaud's phenomenon, an E.S.R. of 107 mm. and a hæmoglobin of 79%. In hospital the E.S.R. maintained a high level and she developed marked proximal muscle wasting. Electromyograms and biopsy showed the changes of polymyositis which was accompanied by twenty-four-hour urine creatine of 680 mg. She subsequently and while on cortisone developed sclerodermatous changes in the skin.

A further case presenting with a rheumatoid type of polyarthritis, was admitted because of severe constitutional disturbance although his E.S.R. at first attendance was only 10 mm. This E.S.R. rose steadily during the first three months in hospital to 65 mm. when he developed a chest lesion characterized by patchy consolidation of one base, fever, a white cell count consistently below 4,000, negative sputum examination and bronchoscopy. While L.E. cells have not been found at any time he has now developed the typical L.E. rash over the dorsum of the hands.

In contrast, reference must be made to the persistently low E.S.R. found sometimes in the type of case we are now recognizing more often, in which a patient with a long-standing rheumatoid type of polyarthritis develops clinical signs of systemic lupus erythematosus.

One such patient of mine with a low-grade polyarthritis of nine years' standing and intermittent leg ulceration developed a pleural effusion at which time L.E. cells were found. She subsequently developed a typical rash on the palm of one hand but throughout her illness to date her E.S.R. has not exceeded 30 mm. She has shown no signs of renal involvement and she is in fact very well. There can be no doubt of the diagnosis of this patient who supplies evidence that lupus erythematosus as defined by the presence of L.E. cell phenomenon and by the classical clinical signs can be a chronic illness with a far better prognosis than formerly implied by this diagnosis.

In conclusion, therefore, it would seem that the E.S.R. and to a lesser extent, the hæmoglobin level have a real place in the diagnosis of rheumatoid arthritis. They are, however, a poor index of the prognosis of joint function and of the presence of accompanying systemic changes which are important in that they may lead to revision of the diagnosis, although perhaps not always the prognosis. To these routine investigations has now been added Rose's test, which because of its relative specificity has, I believe, a useful place in the diagnosis of this disease. Indeed, it is to tests of this sort and the L.E. cell phenomenon that we must turn to sort out the semantic confusion that surrounds the diagnosis of this group of disorders—a confusion to which clinical use of the term "rheumatoid disease" may well add unless it is clearly defined or perhaps allowed to replace the term "rheumatoid arthritis" entirely, thus ignoring the characteristic lesion in the vast majority of cases.

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Dr. L. E. Glynn, Dr. E. J. Holborow and **Mr. G. D. Johnson** (Special Unit for Juvenile Rheumatism, Canadian Memorial Hospital, Taplow, Bucks.): ***The Nature of the Rose-Waaler Factor***

Waaler in 1940 and Rose *et al.*, in 1948, independently reported that in the majority of patients with rheumatoid arthritis the serum contained a factor that potentiated the agglutination of sheep cells previously coated with a sub-agglutinating-dose of rabbit anti-sheep serum. By various refinements the test has been improved so that it has been claimed to give a positive reaction in over 90% of cases. It is, therefore, of great interest to determine the nature of the serum factor responsible.

A consideration of the literature on modifications of the test, which is shown in an abstracted form in Tables I and II, leads to the conclusion that a positive result, independent

TABLE I.—MODIFICATIONS OF THE ROSE-WAALER TEST

Variations of the Detector System

Author	System	Probable Coating
Waaler (1940)	Sheep cell + rabbit anti-sheep cell antiserum	Rabbit γ-globulin
Lamont-Havers (1955) ...	Streptococci + anti-strep. antiserum ...	Human γ-globulin
Heller *et al.* (1954) ...	Sheep cell (tanned) + Human FII ...	Human γ-globulin
Singer and Plotz (1956) ...	Polystyrene latex particles + Human globulin	Human γ-globulin
Fox *et al.* (1953)	Sheep cell + guinea-pig anti-sheep cell serum	G-pig γ-globulin
Waller and Vaughan (1956)	Human Rh+ cells and human incomplete Rh antiserum	Human γ-globulin
Greenbury (1956)	Human group A cells + rabbit anti-group A antiserum	Rabbit γ-globulin
Foz and Batalla (1956) ...	Brucella + human incomplete anti-Brucella antiserum	Human γ-globulin
Hobson and Gorrill (1952) ...	Sheep cell + horse anti-sheep cell serum	Horse γ-globulin
Vaughan (1956)	Immune precipitate of egg-albumen—rabbit anti-egg albumen serum ...	Rabbit γ-globulin

TABLE II.—MODIFICATIONS OF THE ROSE-WAALER TEST

Fractionation of the Serum under Test

Author	Method	Fraction
Svartz and Schlossman (1954)	Cold-precipitated globulin	γ-globulin
Ziff *et al.* (1956)	Euglobulin pptd. by dialysis ...	α-, β- and γ-globulin
Rose *et al.* (1948)	Electrophoretic separation	β-globulin
Thulin (1955)	Paper electrophoresis	β- and fast γ-globulin
Heller *et al.* (1955) ...	Alcohol fractionation. Fraction III ...	73·1% β-, 7·4% γ-globulin
Robinson *et al.* (1954) ...	Sodium sulphate fractionation ...	Mainly β-globulin
Lamont-Havers (1955) ...	Water precipitation	γ-globulin
Lospalluto and Ziff (1956) ...	Cellulose ion exchange and electrophoresis	γ-globulin

of the method used, depends upon the interaction of the Rose-Waaler factor with a γ-globulin. The simplest explanation of the observed facts, however, is that the globulin with which the factor reacts is in some way altered. In view of the observation that the γ-globulin involved can be obtained from any of several different species the interaction must be regarded as occurring between the factor and non-specific groupings common to the γ-globulins of many species. Since, in the majority of the tests, the γ-globulin is pre-combined with some specific antigen, it suggests that these non-specific groupings are exposed as a result of unfolding of the coiled γ-globulin consequent upon its interaction with specific antigen. This unfolding is shown diagrammatically in Fig. 1.

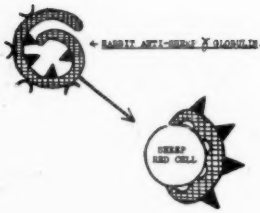


FIG. 1.—Diagram showing the coiled state of the free antibody molecule and the manner in which it is postulated that it uncoils when it reacts with its specific antigen.

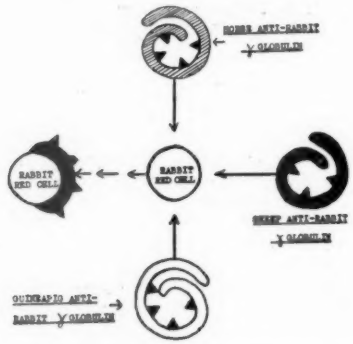


FIG. 2.—Diagram of hypothetical antibody molecules from four different species to show how common non-specific groups could be exposed as a result of the interaction of the antibody with the antigen.

If the above hypothesis be correct then it should be possible to show that there is a signif- cant cross reaction between antibodies to unfolded γ-globulin of species A with simil unfolded γ-globulins of species B, C, D, &c. Fig. 2 shows diagrammatically how the commo grouping might become exposed when, for example, agglutinating antibody from fo different species reacts with rabbit red cells. To test the hypothesis, rabbits were immunized b intravenous injections of rabbit red cells suspended in saline after agglutination by the natural occurring antibodies in sheep, human, horse and guinea-pig sera respectively. The exte to which the antibodies so produced cross-react when brought into contact with antibod combined with its specific antigen was tested by using each of these sera as a Coombs seru to agglutinate human O Rh D +ve cells pre-treated with incomplete anti-D. The result are shown in Table III. Since such a degree of cross-reactivity could not be expected to occu

with free globulin the results must be interpreted as showing the exposure of common non-specific groupings when the antibody reacted with its antigen, in this case the anti-D globulin with the D groupings, on the red cells.

The appearance in the serum of rheumatoid arthritics of a factor with properties similar to those induced in the rabbit sera in the above experiments suggests that it, too, is an antibody to the non-specific groups of immune γ-globulin. It is, therefore, to be regarded as a form of auto-antibody; not to a normal body constituent but to one already modified by a form of denaturation.

TABLE III.—REACTION OF RABBIT ANTISERA TO GLOBULINS OF DIFFERENT SPECIES WITH HUMAN RED CELLS SENSITIZED WITH INCOMPLETE ANTI-D SERUM

No.	Rabbit antisera to	Agglutination titre with human red cells	
		Unsensitized	Sensitized
1	Human globulin	128	1,024
2	,, ,, ...	32	1,024
3	Horse ,, ...	—	1,024
4	,, ,, ...	—	1,024
5	Sheep ,, ...	2	512
6	,, ,, ...	—	1,024
7	Guinea-pig globulin ...	—	64
8	,, ,, ...	—	64

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Professor D. H. Collins (Sheffield): I agree with Dr. Tegner that the diagnosis of rheumatoid arthritis can sometimes be made from nodule biopsy; once, in my own experience, even a few months in advance of clinically manifest arthritis. The lesion of granuloma annulare, though usually more superficial, is the one common source of confusion. The synovial lesion of rheumatoid arthritis, fulfilling the criteria previously enunciated (Collins, D. H., 1949, *Proc. R. Soc. Med.*, **42**, 731) is really very characteristic, but I prefer to use the words "rheumatoid type of synovitis" in the biopsy report, leaving the clinician the right to his own convictions about what is or is not rheumatoid arthritis.

The symposium has shown some of the ways in which we are learning more about the nature and mechanism of a mysterious disease. Unfortunately we are still far from having any information about its cause or causes. Much intellectual effort can be wasted talking about hypothetical "collagen diseases" and mutually comparing rheumatoid arthritis, disseminated lupus, systemic sclerosis, polyarteritis and so forth, because one can only

compare an unknown with other unknowns. The methods of morbid anatomy and histology have probably never revealed the cause of any disease without the pathologist considering collateral evidence or being able to compare the unknown with something that is known.

Dr. Brian Lacey (The John Burford Carlill Pathological Laboratories, Westminster School of Medicine):

Knudsen and Thomas (1957) recorded raised red cell potassium levels in rheumatoid arthritis. Besides its intrinsic interest for those studying pathogenesis, this finding seems likely to prove of great help, complementary to that given by serological and histological examinations, in sorting out these conditions.

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Dr. John H. Glyn (The Arthur Stanley Institute): One speaker has stated that the presence of L.E. cells in a patient's blood is conclusive evidence that the patient is suffering from systemic lupus erythematosus. As clinicians, I think we are entitled to challenge this conception since we are all familiar with cases of chronic and typical rheumatoid arthritis where this phenomenon is found coincidentally. In such cases it has not seemed to bear sinister prognostic implications so far. A recent study of this test by Kievits *et al.* (1956) arrived at a similar conclusion in relation to individual cases.

We have indeed been studying one very interesting patient who attended out-patients for a check-up following a short period of vague rheumatic symptoms. She was concerned about these symptoms because her sister had recently died of systemic lupus erythematosus. In the last year L.E. cells have been found in this girl's peripheral blood on four separate occasions and during this period she has been devoid of symptoms or physical signs. We are naturally watching this patient very carefully.

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Dr. H. J. Gibson (Bath): It was interesting to note that Dr. Cruickshank found focal lesions in muscle to be among the most frequent extra-articular abnormalities in his post-mortem series. It is nearly ten years since I put forward evidence that rheumatoid myositis was part of the disease in a high proportion of cases. Many workers since then have regarded the lymphorrhages as "non-specific". Does Dr. Cruickshank consider the focal lymphocytic lesions in muscle to be as much a part of rheumatoid disease as the lymphocytic foci of the synovial membrane?

Dr. L. E. Glynn has put forward evidence that the antigenic quality of an antibody is modified by attachment to its antigen and that the Rose-Waaler factor may be an auto-antibody. How does he explain the many examples which have been found of antibodies which do not act as sensitizers for the Rose-Waaler system?

Dr. D. A. Brewerton (King's College Hospital) stressed the importance of muscle involvement. In a recent clinical survey of hand deformities, 13% of 300 patients had contractures of the intrinsic muscles of the hand. One of these patients had presented with muscle contractures before there was clinical or radiological evidence of joint involvement. In the same series 64% of the patients had clinically demonstrable tendon lesions in the hands.

Section of Dermatology

President—Louis Forman, M.D., F.R.C.P.

[*February* 21, 1957]

Still's Disease with Pseudoxanthoma Elasticum.—Stephen C. Gold, M.D.

S. O., aged 9 years and 10 months, developed Still's disease at the age of 14 months, starting with pain in the right knee, fever, lymphadenopathy and rash. There was also some swelling of the feet and hands. There was a further period of activity at the age of 3½ years, with abdominal pain (laparotomy was performed, with negative findings) and with the later development of pericarditis, fever, polyarthritis and anæmia (hæmoglobin 58%). She made a satisfactory response to cortisone therapy.

She was first admitted to the Special Unit at Taplow under the care of Dr. E. G. L. Bywaters in 1952, with an acute relapse of the arthritis and fever. There was also lymphadenopathy, a typical Still's rash, high erythrocyte sedimentation rate and an iron refractory anæmia. She was discharged symptom free, taking cortisone 37·5 mg. daily with aspirin. The cortisone had to be reduced following a wedge fracture affecting the eighth thoracic vertebra in November 1954, and finally it was stopped following a hæmatemesis in January 1955. In May 1955 the patient went into a remission following an attack of measles.

She was readmitted in July 1956 with pericarditis, acute arthritis, a Still's rash, fever, leucocytosis and a severe anæmia. The erythrocyte sedimentation rate was 110 mm. in the first hour (Westergren). Butazolidin treatment produced no improvement, and in October she was put back on to hydrocortisone systemically, on which she made a rapid improvement. At the present time she is virtually symptom free, despite continued activity of the disease. At the moment she is taking 40 mg. of hydrocortisone daily and is having active physiotherapy. The joints which are involved are the cervical spine, temporo-mandibular, elbows, wrists, hips, knees, ankles and feet. The hæmoglobin is now 87%, and her erythrocyte sedimentation rate 80 mm. in the hour.

Pseudoxanthoma elasticum.—On July 19, 1956, at a time when the Still's disease was very active, her lips and face swelled up, followed by apparent whealing at the sides of her neck and bends of her elbows. These erythematous lesions itched severely, and persisted for a few days before a well-defined area with serpiginous edges became apparent; there was a surrounding erythema. Within a week the central area became moist and raw, and a few other lesions developed on both forearms. There was a serosanguineous discharge from the centre of these lesions, which, when they started to heal, became less irritable and appeared scaly. When first seen by me (S. C. G.) the areas involved showed a yellowish discoloration, with some superficial scarring at the sites that had previously discharged. The surface resembled chamois leather, and the distribution and general appearance suggested a clinical diagnosis of pseudoxanthoma elasticum. In spite of a negative family history and absence of other signs confirmatory of this disease, a biopsy specimen of skin was taken, and revealed, histologically, changes compatible with pseudoxanthoma elasticum.

Comment.—So far as I have been able to ascertain no similar case has been recorded. It is an important point to realize that the apparent pseudoxanthoma elasticum developed when this patient's Still's disease was at its height and the skin process appeared to become less acute as the Still's disease was controlled by steroid therapy. It is unusual to see ulceration and discharge in pseudoxanthoma elasticum but this has been recorded and is generally in association with marked calcification of the dermis. To-day, the skin appearances are hardly characteristic of pseudoxanthoma elasticum. The yellowish colour is scarcely apparent, but signs of previous ulceration are still to be seen.

Dr. **H. Haber:** This is a very unusual case from the clinical point of view. Histologically, however, one has to accept the case as pseudoxanthoma elasticum. The corium exhibits marked cellularity due to inflammatory changes. Stain for elastica reveals the characteristic changes found only in this condition. The elastica shows fragmentation and curling of its fibres. Silver stain reveals the elastica to be heavily calcified.

The **President:** Pseudoxanthoma elasticum may have a systemic distribution with subsequent sclerosis affecting the heart and blood vessels of the limbs and the viscera. As far as I know, the connective tissue of the joints has not been involved.

It has been suggested that the altered fibres in pseudoxanthoma elasticum are in reality degenerated collagen which takes up the elastic fibre stain (Hannay, P. W., 1951, *Brit. J. Derm.*, **63**, 92).

If this were so in this case, it would indicate a relationship to the collagen changes in Still's disease.

Dr. F. F. Hellier: I do not think that this condition is a true pseudoxanthoma elasticum but that it is some other abnormality of the elastic tissue which gives a similar histological appearance.

Dr. P. J. Hare: I wonder whether there is any evidence that this is a fatty degeneration of elastic tissue which would readily calcify and whether it could act as a cause of the inflammatory reaction which is so striking in the section.

Xeroderma Pigmentosum.—STEPHEN C. GOLD, M.D.

This young woman of 24 recently arrived from Cyprus. Her parents were aware of abnormal freckling of her skin on the areas exposed to bright light since early childhood, and at various periods as she grew up, nodules appeared which have been destroyed by various local means. There is no family history of such a condition, and there is no consanguinity of her parents.

When she attended St. John's Hospital for Diseases of the Skin in December 1956 she presented a classical appearance of xeroderma pigmentosum on the face, neck, dorsal surfaces of her hands, and forearms. There was marked freckling, patchy atrophy and some telangiectasia throughout these areas, while scattered, particularly on the face, were small, crusty lesions suggestive of keratomata, rodent ulcers; there was one larger lesion under the left eye, elevated and dark, apparently increasing in size more rapidly than any other, which clinically suggested the diagnosis of malignant melanoma. There has also been some recent tendency of this lesion to bleed on trauma.

Several biopsies have been performed, and the large lesion has been completely excised. Histologically, the clinical diagnosis of the various tumours was confirmed. The large one proved to be a malignant melanoma, and in the same biopsy specimen there was evidence of a rodent ulcer at the edge of this malignant melanoma. There were many keratomata, as well as small rodent ulcers. Most of these have been removed, but there are one or two still awaiting attention.

This case is presented because it is so typical and also to stimulate discussion on the future handling and on any recommendations which should be made in order to discourage further tumour formation.

Dr. H. Haber: Xeroderma pigmentosum is a condition due to extreme intolerance of the skin to sunlight. White people living in tropical countries show similar changes when their skin breaks down after a prolonged exposure. But even in these cases one has to postulate individual tolerance to light as shown by different degrees of damage produced by people living under similar conditions in the tropics.

The changes produced consist of atrophy, hyperkeratosis and disturbance of pigmentation. Malignant changes in form of keratomas, basal cell epitheliomas and squamous cell epitheliomas are features of the condition. Pigmentary changes lead to freckles, the formation of lentigines, malignant lentigines and malignant melanomas.

Sections of this case show ample evidence of the outlined changes.

Dr. F. F. Hellier: I would like to refer to an interesting case under Dr. J. T. Ingram's care which is somewhat similar to this. It is a young girl who shows multiple appalling tumours on her face but this girl is a complete albino so that her face is quite white. Section of one of the tumours has shown it to be a basal cell carcinoma but it is probable that others are squamous epitheliomata. The condition seems to be a form of xeroderma pigmentosum without pigment. She is to have surgical treatment but this has been delayed because her hæmoglobin is only 19%.

Xeroderma Pigmentosum.—H. SCHWARTZ, M.D. (for HUGH GORDON, M.C., F.R.C.P.).

Miss G. T., aged 17.

This patient was first noted to have a generalized mottled pigmentation shortly after birth. Her brother, four years older, was also considerably freckled but the degree was much less and the onset later in life.

She first attended the Royal Marsden Hospital in 1946 for X-ray treatment of an epithelioma near the left angle of the upper lip (Figs. 1 and 2). Further epitheliomata on the face were successfully treated also by X-rays in January 1948, September 1948, and August 1951. A lesion on the left calf was excised in 1951 and another from the right shin in 1953.

A recurrent and occasionally painful inflammation of the conjunctivæ has existed since 1951 and has been resistant to treatment.

Since 1948 (Figs. 3 and 4) she has been wearing a cosmetic light screening cream compounded by Dr. D. W. Smithers and Mr. J. H. Wood (Chief Pharmacist at the Royal Marsden Hospital):

	%
Titanium dioxide ..	25
Magnesium stearate ..	12·5
Butyl stearate	12·5
Menthyl salicylate ..	20
Pigment base	2
Vanishing cream ..	28



FIG. 1.—November 1946, aged 6.



FIG. 2.—November 1946, aged 6.



FIG. 3.—June 1949, aged 9.

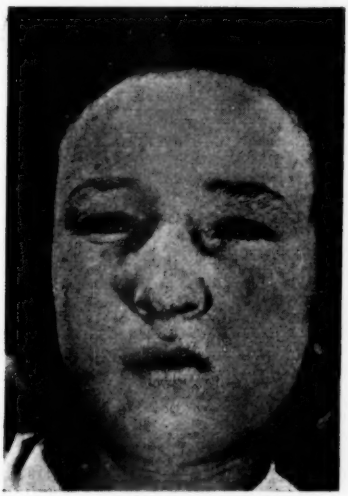


FIG. 4.—July 1951, aged 11.

Figs. 2 and 4 are reproduced from Smithers and Wood (1952) by kind permission.

Comment.—This patient's maternal and paternal grandfathers were brothers and her mother and father therefore were first cousins. In 1952, Smithers and Wood published details of the case under the title "Xeroderma Pigmentosum. An attempt at cancer prophylaxis", and she is being shown to demonstrate the continued effectiveness of the cover cream compounded by them and now manufactured commercially. I believe the cream currently in use also contains 2% of iso-butyl-para-amino benzoate, but it is my opinion that its light screening efficacy is more related to the high powder content (titanium dioxide) acting as a mechanical barrier to light rather than to the alleged light absorbing properties of the other contained compounds.

Since she began using her cream only one epithelioma has developed on a cream-protected area, although two others occurred on parts of the body much less exposed to light.

REFERENCE.—SMITHERS, D. W., and WOOD, J. H. (1952) *Lancet*, , 945.

Dermatomyositis.—B. SCHWARTZ, M.D.

Mrs. I. N., aged 44.

In November 1956 this patient, who had no previous history of skin disease, was referred to Dr. Stephen Gold because of the development, following a tooth extraction two weeks previously, of an irritating skin rash over the arms, chest, thighs and hands and some puffiness of the face and pains in the legs.

Past medical history.—A left radical mastectomy with bilateral oophorectomy was performed in April 1956 and the sternal and axillary areas were subsequently subjected to deep X-ray therapy.

On initial examination.—She was afebrile and showed: (1) Pronounced erythema with some telangiectases symmetrically placed over the chest, thighs and arms with streaky lesions over the dorsum of the fingers and telangiectases around the nail folds. (2) Swelling of the periorbital tissues. (3) Marked muscular weakness of the limbs and back.

A diagnosis of dermatomyositis was made and she was admitted to hospital for further observation.

Investigations.—Urine: No abnormality. Blood pressure 125/95.

Blood count: Hb 96% (14·2 grams per 100 ml.); W.B.C. 5,800; P. 63, L. 31, M. 5, B. 1%. No L. E. cells were seen in the peripheral blood.

Blood urea: 22 mg. per 100 ml.

Total serum proteins: 7·6 mg. per 100 ml.; albumin 3·3 mg. per 100 ml. Globulin 4·3 mg. per 100 ml.

A muscle biopsy from the right deltoid area showed no significant abnormality.

Treatment with prednisone 40 mg. daily resulted in rapid improvement in appearance and muscular power but there has been some recurrence since the drug was inadvertently discontinued.

Comment.—This adds further to the already growing number of cases where the occurrence of dermatomyositis has been associated with malignant disease, the initial lesion here being a spheroidal cell carcinoma of the breast.

Dr. S. Gold: This patient presented a very characteristic picture of an œdematous and red face, with linear erythema on the backs of her hands and muscle weakness of her trunk and thighs. Her breast was first removed some months ago, followed by a bilateral oophorectomy. Subsequently, following some dental treatment, the dermatomyositis developed dramatically. The question of the administration of steroids is an interesting one. The use of prednisone has certainly suppressed this patient's symptoms of dermatomyositis in the most satisfactory manner; I understand that there is nothing to suggest that the use of steroids would encourage secondary metastases.

Dr. F. F. Hellier: I should like to ask whether anyone has had experience of *transaminase*. This is an enzyme which occurs in the blood-stream when muscles are damaged and has been estimated in cardiac infarction. It gives some indication of the amount of damage to muscle in the heart and it is being used at the Mayo Clinic to estimate the activity of the disease process in dermatomyositis. It is important to know when this condition is active and when it is burnt out, if one is using steroids, as obviously one does not want to go on with them for an unnecessarily long time.

The following cases were also shown:

Acro-keratosis Verruciformis.—Dr. ARTHUR ROOK and Dr. DANILO STEVANOVIC.

? Neuro-fibroma.—Dr. PATRICK HALL-SMITH.

(1) Necrobiosis Lipoidica, (2) Leuconychia Congenita, (3) Nævus of Ota, (4) Porokeratosis (Mibelli).—Dr. STEPHEN GOLD.

Benign Mucous Membrane Pemphigoid.—Dr. LOUIS FORMAN.

Section of Experimental Medicine and Therapeutics

President—Professor C. A. KEELE, M.D., F.R.C.P.

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Chemical Causes of Pain and Itch

PRESIDENT'S ADDRESS

By Professor C. A. KEELE, M.D., F.R.C.P.

PAIN and itch are unpleasant sensations which are readily distinguished from other cutaneous sensations such as touch and temperature, and can usually be distinguished from each other, particularly because cutaneous pain leads to reflex withdrawal, and itching provokes the desire to scratch.

Both sensations can be elicited by physical and chemical stimuli and several investigators, e.g. Rothman (1941, 1954) and Bishop (1946, 1948), have pointed to numerous factors which pain and itch have in common. After leaving the skin the nerve pathway mediating itch runs to the spinal cord and accompanies the fibres subserving pain in ascending the antero-lateral tracts. Bickford (1937–38) showed that cordotomy abolished both pain and itch, but not touch, and he observed similar sensory dissociation in patients with syringomyelia. Critchley (1956) has reported that in persons with congenital indifference to painful stimuli itching is also absent.

There is also much evidence, from common experience and from experimental studies, showing a close functional relation between pain and itch. Many stimuli to the skin can produce itch when the intensity is low and pain when the intensity is high. Bishop (1946) applied electrical stimuli to a single pain spot and reported that passage of a weak constant current, or repeated weak shocks, produced itch, whereas a stronger stimulus produced pain. Hardy *et al.* (1950) found that prolonged application of heat at an intensity below threshold for pain, produced itching. It has therefore been suggested that itch is, in fact, subthreshold pain.

Lewis *et al.* (1927–29) attributed the itching produced by such physical stimuli to the release of histamine or H-substance. However, it is by no means clear that the production of itch by low intensity physical stimulation is always chemically mediated, and where such stimuli produce itch without obvious vascular changes in the skin it is difficult to exclude a direct action on the appropriate nerve receptors.

Other points of resemblance have been made by Hardy *et al.* (1952). They have gone farther than Lewis in ascribing two qualities to superficial pain, namely pricking and burning, and have reported that pricking pain is abolished by ischæmia before burning pain. They have also distinguished pricking and burning types of itch, and suggest that *pricking* pain and itch are conveyed by fast-conducting nerve fibres and *burning* pain and itch by slow-conducting fibres.

A most important factor influencing the occurrence of pain is *hyperalgesia.* When tissues are damaged the sensitivity of pain nerve endings increases and normally subthreshold stimuli become painful. Hardy *et al.* (1950) have distinguished between the *primary* hyperalgesia of the actually damaged tissues, in which pain threshold is lowered, and the surrounding *secondary* hyperalgesia in which pain threshold is normal but the response to a painful stimulus is exaggerated. The secondary hyperalgesia corresponds to the spreading nociensor tenderness of Lewis, but Wolff attributes it to changes within the spinal cord induced by stimuli from the damaged area. Bickford noted that when itching was induced in the skin by a gnat bite or by histamine, the area of *spontaneous* itching was surrounded by a much larger area of *itchy* skin in which itching was very readily set up by light friction. The itchy skin corresponds to the secondary hyperalgesia just referred to and is likewise attributed to activity in the spinal cord.

Now although pain and itch have much in common they are in many ways mutually exclusive. When pain occurs spontaneous itching is depressed or abolished, provided the

pain stimulus is applied within the area of itchy skin. This is the rationale of scratching. Further, in an area of primary or secondary hyperalgesia neither spontaneous itch nor itchy skin can be established.

In certain respects pain and itch are quite distinct from each other. (1) Each has its own peculiar quality, and has a wide range of intensity from the just perceptible to the completely intolerable, and as Lewis pointed out both may be experienced simultaneously. (2) Superficial pain leads to reflex and voluntary evasive movements and itching to scratching movements. (3) Lewis noted that immersion of skin in water at 40–41° C. alleviated itching but aggravated burning pain. (4) Morphine, while relieving pain can actually make itching worse, whereas the converse is true of the barbiturates. (5) Itch cannot be elicited from skin after removal of the epidermis.

Lewis (1942) was not only convinced that itch and pain are separate phenomena, but also wondered whether superficial and deep pain should not be regarded as different sensations. I shall return later to the relation between depth of receptors and type of sensation, in the light of our own work on pain-production by chemical agents.

Chemical Factors in the Production of Pain

The production of pain by chemical factors has been little studied experimentally because it is difficult to make repeated applications of the substances under investigation, and to obtain accurate measurements of the results. We know of course that surface application of strong irritants such as chloroform, acids and alkalis, produces severe and painful damage in the skin and mucous membranes, and that injected solutions of certain drugs, such as organic arsenicals and mercurials, and of hypo- or hypertonic solutions will produce pain in both skin and deeper structures. Other examples of *extrinsic* pain-producing materials are nettle stings and certain venoms, such as wasp venom, which I shall mention later.

It is, however, more important to consider the possibility of pain-production by *intrinsic* chemicals, substances derived from living body fluids and tissues. Consider, for example, the pain of *peptic ulcer*. It is natural to suspect that pain in this condition is due to the action of the acid gastric juice on the ulcerated surface, and the relief of this pain by administration of antacids supports this view. Moreover, Palmer (1926), and Bonney and Pickering (1946–48) have reported that administration of HCl at pH of 1–2 produces pain in many patients with ulcer, and that when spontaneous ulcer pain occurs the pH of the gastric contents is markedly acid.

To take another illustration—the pain and tenderness in *ischæmic muscle*. MacWilliam and Webster (1923) suggested that the pain which develops when muscles are worked under ischæmic conditions might be due to metabolic products of activity. Lewis *et al.* (1931) developed this view and postulated a "factor P" as the stimulus to pain. Factor P is presumed to arise from metabolic activities in muscle fibres and to diffuse thence to the extracellular space where stimulation of pain nerve endings takes place. The steady increase of pain during ischæmic muscular work is attributed to accumulation of factor P in the tissue spaces, and the very rapid relief which follows restoration of the circulation to the speedy dispersal of this substance. Lewis did not identify factor P and suggestions by others that it is lactic acid or potassium have never been confirmed.

The chief interest in this type of pain lies in the explanation which it offers for the pain which accompanies activity in skeletal and cardiac muscle in the presence of obstructive arterial disease. The pain of intermittent claudication in the limbs, and of angina pectoris, are both typically provoked by exertion and relieved by rest. With sudden complete occlusion of an artery, as in coronary thrombosis, the onset of pain is similarly produced but it cannot, of course, be relieved by rest.

Inflammation is another state in which it has been postulated that pain is provoked by chemical agents. Dolor was one of the cardinal features of inflammation mentioned by Celsus, the others being rubor, calor and tumor. Whilst much work has been done on the factors which may account for the vasodilatation and increased permeability of the inflammatory response, much less attention has been paid to the processes by which pain arises in this state, though it is commonly said that the pain is due to increased tension in the inflamed tissues. Now whilst there may certainly be an increased tension in an inflamed area this factor cannot directly provide more than a partial explanation since the outstanding feature of an inflammatory process is the marked *hyperalgesia* which it induces. In inflamed tissues the pain threshold is much reduced and stimuli which are not painful in normal tissues may be very painful in the affected region. The hyperalgesic state may be such that even arterial pulsation can produce a severe throbbing pain with each heart beat.

Sometimes an inflamed area is spontaneously painful, that is pain is present without application of an external stimulus, or when the inflamed part is completely at rest. Lewis (1942) suggested that in such cases the chemical agents which produce hyperalgesia have reached a sufficiently high concentration to stimulate the pain nerve endings on their own.

One of the examples which Lewis gave to support the idea of chemically induced pain was the delayed pain which follows a heat burn. After the intense physical stimulus of the heat the sharp peak of pain often subsides to zero, and then after 15–60 seconds pain returns, builds up to a moderate intensity within a few minutes, and then slowly subsides again. After this there is no more spontaneous pain but there is frequently hyperalgesia. The subsequent hyperalgesia resembles that produced by other forms of injury such as occurs after excessive cooling (−15° C.), exposure to ultraviolet light, scratching and infective and allergic inflammatory processes.

Lewis showed that when there was cutaneous hyperalgesia following injury spontaneous pain could be aroused either by warming the skin to 30–35° C. or by occluding the circulation to the affected part. He suggested that in both these cases the spontaneous pain was produced by an increased local concentration of metabolites, the raised temperature increasing their production and the ischæmia preventing their removal. However, as pointed out by Nathan (1953) occlusion might act by increasing the sensitivity of the pain nerve fibres, so that pain could occur without any increase in concentration of pain-producing metabolites.

So far there have been no suggestions as to what these metabolites are. Lewis merely said that he did not think histamine was concerned. He found that aqueous extracts of skin caused pain on intradermal injection but did not identify the active principle.

Experimental Work on Pain-producing Substances.

At the Middlesex Hospital Medical School, with my colleagues Miss Desirée Armstrong, Dr. J. B. Jepson and Dr. J. W. Stewart, we have been investigating the possible role of intrinsic chemical factors in the production of cutaneous pain with particular reference to substances which develop in blood (Armstrong *et al.*, 1957).

In conjunction with Drs. Dry and Markham (Armstrong *et al.*, 1953) we first studied various methods for producing pain by chemical agents. Lewis had administered histamine and other substances by *pricking through a drop of solution* placed on the skin, but we soon found that this mode of application was unsatisfactory since pain was not produced by substances which were very active when given in other ways. We also tried *intradermal injection* which was certainly effective with most substances which we tested. However, we sometimes observed irregular responses, such that isotonic saline might occasionally be painful and normally painful solutions ineffective. Of course, with sufficiently numerous injections such irregularities could be taken account of, but our subjects (I was one of them!) did not seem to enjoy receiving the large number of injections needed to give statistically significant results. Further, it was obviously dangerous to inject inflammatory exudates which might be contaminated with bacteria or foreign materials to which the subjects might become sensitized. So we developed what was for our purposes a better method, in which the substances to be tested are applied to the exposed base of a blister produced by cantharidin.

Blister area.—Cantharidin plaster, 0·3% and about 1 cm. in diameter, is applied to the skin of the forearm for four to six hours in the evening. By the next morning a blister has usually developed. The fluid (about 0·2 ml.) is aspirated, the raised epidermis is removed and the base of the blister is then available for testing. Dr. J. Boss has shown that all but the basal epidermal cells are removed and that the cells of this layer tend to be separated from each other though still attached to the basement membrane. The nerve fibres which end in the epidermis will be ruptured during blister formation but deeper nerve terminals will remain intact.

The area is bathed in Locke's solution which does not produce pain. This solution is removed at intervals (usually ten minutes) to allow application of the test materials. We have found this technique to be very reliable and sensitive, and the effect of a given solution is reproducible during an experimental session lasting one and a half to two hours. The subject of course does not know the nature of the applied materials and on some occasions the experimenter has also been kept in ignorance.

We are aware that the blister base is not a normal tissue and that it might be hypersensitive to certain agents, but since pain often occurs in already damaged tissues the conditions of our tests are reasonably relevant. The constancy of response to a given concentration of a standard agent is of great value in assessing the rise and fall in activity of labile pain-producing fluids such as inflammatory exudates and plasma. Solutions need not be sterilized as they are rapidly removed, but we have naturally avoided heavily contaminated materials.

We have obtained much useful information from the blister area which has most of the advantages of an isolated organ preparation combined with the very unusual property of remaining attached to the rest of the body.

I will now describe the effects of various pain-producing agents as tested on the blister area.

Acetylcholine (ACh).—When different amounts (in Locke's solution) are applied to the blister area pain is produced with concentrations from 10^{-5} g./ml. upwards. The pain is commonly immediate in onset, smarting or stinging in character, rapidly reaches a peak and then subsides to zero within 30–60 seconds. The effects of different doses are graded.

Potassium chloride.—Solutions, from 0·1 to 1%, produce pain rather similar to that seen with ACh but the effect comes on a little more slowly and lasts rather longer.

Tonicity.—Marked deviations from physiologically normal osmotic pressure also produce pain. With decreasing concentrations of NaCl pain occurs at about 0·3% NaCl and with increasing concentrations at about 3% NaCl.

Acidity.—When acid solutions are applied to the blister area pain is not produced until the pH falls to about 3–3·5.

Histamine.—The part played by histamine in tissue reactions, and claims by Rosenthal that it is the mediator of cutaneous pain led us to test this substance on the blister area.

Briefly, we have found that in concentrations of 10^{-5} g./ml. or higher it can produce transient pain (which is sometimes severe with 10^{-3} g./ml. concentration) the pain being followed by itching. Itching alone occurred with concentrations from 10^{-5} to 10^{-7} g./ml. Whenever there were sensory effects weal and flare were also seen.

It is difficult to know whether histamine release in skin or other tissues ever produces concentrations high enough to cause pain. Certainly, the classical instance of *in vivo* release of histamine, namely the urticarial weal, is accompanied not by pain but by itching. However, one cannot exclude the possibility that with more severe tissue damage, high, pain-producing concentrations of histamine might be released at first, but in these circumstances other pain-producing agents might also be present.

Substance in Inflammatory Exudates

In the course of our earlier work we collected the fluid from the blister into a glass tuberculin syringe and in some experiments we reapplied this fluid to the exposed blister base, at first regarding this as a control application. However, we were surprised to find that on many occasions the blister fluid produced marked and prolonged pain after a latent period of 15–45 seconds. On other occasions blister fluid did not produce pain and eventually we found that when the application was made within one hour of aspiration the fluid was almost invariably painful whereas after one hour it was not. Thus the pain was produced by an unstable constituent of blister fluid.

At first we thought this substance might be 5-hydroxytryptamine (serotonin, 5-HT). We therefore tested blood serum which was known to contain 5-hydroxytryptamine and found that this produced pain similar to that evoked by blister fluid, plasma being negative in these experiments. Platelet extracts also produced pain. By this time we had obtained synthetic 5-HT which produced the same type of pain as blister fluid and serum, 5-HT being effective in concentrations of 10^{-6} to 10^{-7} g./ml. and occasionally at 10^{-8} g./ml.

Now since 5-HT is known to be very active in causing contraction of the isolated rat uterus we applied blister fluid to this preparation and observed uterine contractions. However, we soon found several respects in which the active substance in blister fluid differs from 5-HT. For example, the substance in blister fluid is unstable, but 5-HT is stable in this fluid; the action of 5-HT on the rat uterus is antagonized by dihydroergotamine and lysergic acid diethylamide, that of blister fluid is not; and acetone which extracts 5-HT from protein-rich fluids precipitates the activity of blister fluid with the proteins.

Thus we had found that both serum and blister fluid contained pain-producing agents, that in serum being a stable compound of known structure, namely 5-HT, that in blister fluid being an unstable substance of unknown composition. We then found that the activity of blister fluid could be preserved by deep-freezing which meant that we could keep such fluids until it was convenient to test them.

We still had to consider the question—why is a blister not painful?—for such is the case. To study this point we tested fluid immediately after withdrawal from a blister and found that it did not cause either pain or uterine contraction but that after a short while it did both. Thus the pain-producing, uterus-stimulating activity developed only after collection of the blister fluid into the glass syringe. Blister fluid was inactive *in situ*, and was activated after a few minutes in a glass syringe, the activity reaching a peak after 5–10 minutes and then declining.

We soon found that other *inflammatory exudates* such as a pleural effusion and joint fluid from patients with rheumatoid arthritis behaved just like blister fluid (Argent *et al.*, 1954). Finally we found (Armstrong *et al.*, 1957) that blood plasma responded in the same way. (Our original negative responses to plasma were due to testing more than one hour after collection of the blood, when the pain-producing substance had come and gone.)

Thus it seems likely that the pain-producing activity of inflammatory exudates is due

to their derivation from plasma in which the fundamental process of activation by glass can be much more conveniently studied. Heparin does not affect this activation of plasma. When blood is collected into a siliconed syringe, transferred to polythene centrifuge tubes containing heparin, and spun at 4,000 rev./minute for 15–20 minutes, the upper half of the plasma contains no red cells or leucocytes and very few platelets. Such plasma does not cause pain or contract the rat uterus (we call it "preactive" plasma), but when transferred to glass it is activated exactly as described for the exudates. Thus virtually cell-free plasma can form a powerful pain-producing substance when brought into contact with glass.

And now for the nature of this substance. Using ultrafiltrates, and aqueous and alcoholic extracts of active plasma, we have found that from its physical, chemical and biological properties the pain-producing substance (PPS for short) appears to be a polypeptide, closely resembling the substance "bradykinin" described by Rocha e Silva *et al.* (1949). Bradykinin is made by the action of trypsin or proteolytic snake venom on plasma α_2-globulins. Plasma PPS resembles bradykinin in that it, or something very similar, can be formed by the addition of trypsin to preactive plasma; the proteolytic enzyme of plasma, called plasmin or fibrinolysin, acts in the same way. Activation of plasma by contact with glass or by addition of trypsin or plasmin, is inhibited by the soya bean trypsin inhibitor.

All these findings suggest that the fundamental process in the formation of PPS is activation of a proteolytic enzyme in plasma. The rapid decay of the substance is presumably due to the presence of a peptidase in plasma (Armstrong *et al.*, 1957).

Mediators of Pathological Pain

Next, I shall consider how far these various chemicals can account for pathological pain. It seems to me unlikely that there is a single chemical mediator for all types of pain, and comparisons with the role of ACh or noradrenaline as transmitters, or of histamine in anaphylactic shock, are over-simplifications.

Nettle stings.—Emmelin and Feldberg (1947) showed that nettle stings contain high concentrations of ACh and histamine which could certainly produce the initial stinging pain. The itching and triple response would of course be due to the histamine. Recently, Collier and Chesher (1956) have shown that nettle stings also contain 5-HT in amounts which could produce pain of longer duration. It is also intriguing to hear that Brittain and Collier (1957) have found an antagonist to 5-HT in dock leaves!

But even with three pain-producing agents it is still difficult to explain why the pain following nettle stings may last for some hours. It seems possible that a proteolytic enzyme called solanain, which occurs in nettle stings, might contribute to the picture by forming pain-producing polypeptides from plasma and tissue proteins.

Wasp venom.—Jaques and Schachter (1954) have shown that wasp venom contains, in addition to high concentrations of histamine and 5-HT, a pain-producing polypeptide named kinin. There is no difficulty here in accounting for both pain and local tissue reactions in terms of these substances.

Among other venoms, *bee* venom contains much histamine, but no 5-HT, and *scorpion* venom contains enough 5-HT to produce pain (Adam and Weiss, 1956).

The possible role of the intrinsic pain-producing factors.—This is necessarily speculative as there are no technical means of measuring local release of these substances while pain is occurring. To me it seems most likely that pain resulting from tissue damage could be due to histamine (in high concentration), 5-HT and the plasma PPS, though in the special case of peptic ulcer HCl can play a part, and it would be difficult to exclude the contribution of released potassium from damaged cells.

Histamine would be liberated from damaged mast cells, and perhaps 5-*HT* as well, but release of the latter could arise in another way. Trauma damages capillary endothelium which then becomes sticky. Leucocytes and platelets adhere to the damaged endothelium, the platelets disintegrate and release 5-HT in high local concentration. If blood escapes into the tissues release of 5-HT from platelets would also occur. The work of Beloff and Peters (1945) shows that tissue damage releases an active proteolytic enzyme in skin and if such an enzyme acted on plasma it could form the pain-producing polypeptide. Tissue cells also contain an activator of the proteolytic system of plasma.

It is interesting to note that histamine, 5-HT and the plasma PPS form a mixture almost identical with that found in wasp venom. It is as if such an unholy trinity had been evolved by Nature as the most reliable recipe for pain!

Apart from the production of actual pain by these chemical agents it is probable that all three can also produce hyperalgesia. Another factor which increases the sensitivity of the pain endings is ischæmia of the nerve fibres, so in an area of tissue damage with accompanying œdema there are several influences tending to cause pain.

The hyperalgesia of inflammation underlies the pain associated with many conditions.

The pain of peptic ulcer is determined not only by acid, but even more by the sensitivity of the inflamed ulcer (Kinsella, 1953; Smith, 1955); migraine is due to stimulation by distension of temporal periarterial nerve endings made hypersensitive by plasma PPS (Osterfeld *et al.*, 1955); toothache is due to increased tension in an inflamed pulp. Finally, I would like to suggest that the pain of coronary occlusion is due not only to Lewis' factor P but also to the 5-HT and PPS which will be liberated in the acute inflammatory process, and at the same time the pain nerve endings will be rendered hyperalgesic as the result of ischæmia of the nerves.

Chemical Production of Itch

The first substance one thinks of in this connexion is *histamine*. When Lewis and his colleagues were studying the cutaneous vascular actions of histamine they naturally noted the itching which it produces when pricked into the skin. When the release of histamine or H-substance was postulated as a feature of the response to mild tissue injury or to cutaneous allergic reactions of the urticarial type, the argument was supported by the occurrence of itching in these states. Lewis also noted the itching associated with the triple response provoked by introduction of morphine into the skin and itching has been recorded with other histamine liberators such as tubocurarine, compound 48/80, and certain diamidines used in the treatment of trypanosomiasis.

In *urticaria* itching is a regular occurrence, and it is significant that it is most marked before or during the early phase of development of the weal. This shows that the sensory effect is not due to mechanical distension of the skin. In *dermographia* histamine release is usually unaccompanied by itching. These differences have been attributed by Broadbent (1953, 1955) to differences in the site of liberation of histamine. In urticaria the release of histamine is just beneath or partly in the epidermis, which leads to itching, whereas in dermographia the release occurs deeper in the dermis away from the superficial itch receptors. The deeper nerve endings contain pain receptors which, as already described, are stimulated by high concentrations of histamine. In Lewis' experiments histamine was introduced by pricking through a drop of solution on the surface of the skin. This explains why he recorded itching only, without pain, whereas other investigators have reported that intradermal injection of histamine does produce pain. In our own studies on the blister base histamine probably produces itching by acting on the epidermal receptors in the intact skin surrounding the exposed area, whereas pain results from higher concentrations acting on the receptors in the dermis.

A well-known extrinsic source of itch is "itch powder" or cowhage which consists of the very fine sharp-pointed spicules or trichomes which cover the seed pods of the leguminous plant *Mucuna pruriens*. This plant was first brought to England by Hans Sloane when he returned from the West Indies in 1688, and in the eighteenth century cowhage, taken in honey or treacle, was used in the treatment of roundworms. When rubbed into the skin the powder produces marked itch, both burning and pricking in character and becoming painful at times. Itching can occur without much evidence of cutaneous vasodilatation, but often there is erythema and sometimes weal and flare. The itching is not a mechanical effect due to pricking since previously boiled spicules are not effective.

Broadbent (1953) showed that an extract of cowhage contained very little histamine, but experiments on the cat's blood pressure, the guinea-pig ileum and on human skin suggested that the active principle was a histamine liberator. Subsequently Bowden *et al.* (1954) found that cowhage also contained 5-HT in amounts which, from our experience, could account for the pain which sometimes accompanies its application.

However, more recent studies by Shelley and Arthur (1955) have shown that cowhage contains a proteolytic enzyme, which they call *mucunain*. When this was administered by intradermal injection it produced itching within 30 seconds. They have also used a simple technique for making what appears to be an intra-epidermal injection. By inserting a single cowhage spicule almost parallel to the skin surface they produced itching within 15–30 seconds without erythema or urticaria. The discovery of one pruritogenic proteinase naturally raised the question whether other proteolytic enzymes acted similarly. Arthur and Shelley (1955) have shown that intra-epidermal or intradermal administration of both plant proteinases, such as papain, and animal proteinases, such as trypsin, chymotrypsin and plasmin, can produce itching which from its speed of onset is not due to histamine release. Other types of enzymes were inactive.

This work suggests that within the body two main groups of substances could give rise to itching.

(1) *Histamine*, liberated by injury, drugs or an antigen-antibody reaction in the skin.

(2) *Proteolytic* enzymes, liberated as the result of cellular injury. It is not known whether these enzymes act directly on nerve endings or whether they liberate polypeptides in a manner similar to that described for the pain-producing substance of plasma. Proteolytic

enzymes can of course release histamine from tissues, but Shelley and Arthur's work seems to me to show that they probably cause itch in some other way. We have observed that in addition to their pruritogenic action when applied superficially to the skin, mucunain and trypsin also produce pain when applied to the deeper nerve endings exposed in the blister base.

Another aspect of chemical production of itch is the possibility of *central* itch. So far as I am aware the production of itch by the action of chemical agents on the central nervous system has not been clearly demonstrated in man, However, experiments on cats and dogs have shown that the application of certain drugs to the brain provokes marked scratching. Koenigstein (1948) showed that intracisternal injections of morphine, eserine, pilocarpine or ACh were very active in the cat, and Feldberg and Sherwood (1954) have found that intraventricular administration of diisopropylfluorophosphonate (DFP) and eserine produces signs of intense itching in the same species.

This experimental work in animals raises the possibility that certain types of itching in man might be of central origin, particularly in those instances where itching is widespread and where there are initially no abnormal manifestations in the skin. In the case of morphine, pruritus might be produced by histamine liberation in the skin or by a central action as suggested by the work of Koenigstein. However, it does not seem likely that histamine would be the cause of itching unless there was accompanying vasodilatation and wealing, since Arthur and Shelley (1955) found that after intra-epidermal administration of histamine itching never occurred without these other signs. The relief of itching by antihistamine drugs is, of course, no proof that the cause of itching is histamine release, since these drugs have well-recognized central nervous actions of a depressant nature.

The generalized pruritus of obstructive jaundice, Hodgkin's disease, chronic nephritis or diabetes cannot be explained in terms of any known chemical agent, nor indeed is it known whether the itching is due to a peripheral or a central nervous action. In the case of obstructive jaundice, the fact that bile salts are weak histamine releasers appears to be irrelevant, since Sherlock (1955) has shown that there is no constant relation between itching and the blood cholic acid level, and the itching is not aggravated by intravenous injection of bile salts. Some other, as yet unknown, factor must be involved.

With regard to the itching of skin diseases there is one condition for which one can confidently offer an explanation. I refer to urticaria, in which Lewis' original view that this was the typical lesion of histamine release has been amply confirmed by subsequent work. Antihistamines can prevent not only the itching, but the development of the flare and weal. It is more difficult to point to definite single factors to explain the itching of such conditions as eczema, atopic dermatitis and lichen planus. Histamine could, of course, be involved, so could proteolytic enzymes from the damaged cells, but there is no clear way of determining what part these (or other factors) play in any given case. It would certainly be worth while to study the effects of inhibitors of proteolytic enzymes, for example, the soya bean trypsin inhibitor, on the itching of superficial inflammatory conditions of the skin.

And now to return to the relation between pain and itch. First, something must be said about the histology of the nerve endings in the skin. Weddell and his colleagues at Oxford (Weddell *et al.*, 1955) have shown that nerve fibres end in naked axoplasmic filaments in the epidermis, and at various levels in the dermis. It was formerly thought that free, unencapsulated nerve endings were concerned only with pain, but Weddell's recent demonstrations that all forms of cutaneous sensation can be felt in skin which does not possess specialized encapsulated endings, shows that some of the free nerve endings must be involved in the perception of temperature and touch as well as pain.

Our own work on chemical production of pain and that of others on itch, can be readily linked with a distribution of free nerve endings in epidermis and different levels in the dermis. It seems to me very likely that the *intra-epidermal* nerve endings are concerned only with *itch* and the dermal endings only with *pain.*

The receptors for itch must therefore be situated on the axoplasmic filaments running between, but not into, the cells of the epidermis, penetrating as far as the stratum granulosum. These receptors can be stimulated by histamine and proteolytic enzymes, but not by other substances such as potassium or 5-HT. They can also be activated by mechanical, thermal and electrical stimuli at intensities below those which cause pain, though there may be chemical mediation in these cases. Light contact can certainly stimulate them in itchy skin. When the epidermis is removed itching can no longer be elicited, because the appropriate receptors have gone. Since the occurrence of itching is related to the so-called pain spots on the skin, and since nerve fibres conveying itch run up the anterolateral tracts of the spinal cord, it is assumed that the itch fibres, though independent of pain fibres, pursue the same anatomical pathway. The only differences are at the very periphery, and presumably also in the central nervous system where the pathways end.

With these assumptions it is easy to explain how itch can be felt at all intensities from the just detectable to the intolerable, without any element of pain. One can also explain how pain can be felt even at the lowest intensities without any trace of itch, and how it is quite possible to distinguish both sensations occurring simultaneously. These facts are much more difficult to explain on the assumption that itch is subthreshold pain (Bishop, 1948). It is, of course, true that a painful stimulus can abolish itching but this would seem to be due to a central suppression rather than a peripheral modification of nervous activity.

Lewis was tempted to regard superficial and deep pain as distinct sensations and our work shows that the quality of pain may differ even at different levels in the dermis. On the blister base the typical immediate smarting pain produced by ACh is different in character from the delayed duller pain of 5-HT and PPS. The difference in time of onset suggests that ACh acts on nerve endings right on the surface of the exposed base and that 5-HT and PPS act on deeper nerve endings to which they take time to penetrate. Incidentally, the action of KCl in producing a sensation of warmth shows that receptors other than itch and pain can be chemically activated.

We have not ourselves studied subcutaneous or deeper pain receptors but they probably also show selective sensitivity to chemical and physical stimuli and the pain produced is certainly of a different quality from that evoked in superficial structures.

SUMMARY

I suggest that there are at different depths in the skin, nerve endings which can be differentially stimulated by chemical and physical agents to give rise to different qualities of sensation. The most superficial, the intra-epidermal endings, are concerned with itch, some of the superficial dermal endings with smarting pain (the type of pain which most closely resembles itch in character), and some of the deeper dermal endings with a "duller" type of pain. The nerve fibres coming from the epidermis and different layers of the dermis are distinct from each other but they all run together in peripheral nerve and spinal cord to end presumably in anatomically distinct regions in the brain. This hypothesis suggests that a suitable anatomical substratum exists for the functional activities which I have discussed.

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Section of General Practice

President—JOHN H. HUNT, M.A., D.M.

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DISCUSSION ON THE MODERN OUTLOOK IN THE MANAGEMENT OF PULMONARY TUBERCULOSIS

Dr. K. Neville Irvine:

BCG Vaccination

From my angle the modern outlook in the management of any preventable disease is its prevention. We have all read of the ravages of smallpox before vaccination; in the twenty-four years that I have been in general practice I have myself seen diphtheria practically wiped out by APT; I hope that I may live to see pulmonary tuberculosis similarly reduced to a rare condition by preventive measures.

The ideal method of eradicating tuberculosis is to remove all sources of infection; this is the line taken by our veterinary colleagues in producing tuberculin-negative herds. Unfortunately this is a slow and difficult procedure if you cannot slaughter infectious cases. In the meantime much may be done by protective measures for the uninfected. Better standards of living, less overcrowding and education in hygiene are matters with which we general practitioners deal daily; there is little fresh to discuss here.

In 1949 a new preventive measure was introduced into this country. Under the control of the Ministry of Health, BCG vaccine was released to approved vaccinators for use on especially exposed persons—nurses, medical students, and the contacts of known cases of tuberculosis; it did not enter the realm of general practice. But in 1953 it was released for the mass vaccination of one age-group of the entire population—the 13-year-olds. To-day the family doctor is having rapidly to read up a subject about which he was never taught as a student, so that he can answer the searching questions of anxious parents. It is for this reason that I am confining myself to this one aspect of the prevention of tuberculosis.

When we consider that about every five-hundredth person we meet in a bus is an unknown infectious case of tuberculosis, it is clear that our chances of becoming infected are great. Ninety-nine times out of a hundred our first encounter with the tubercle bacillus results only in a subclinical infection—thanks to our natural resistance. This subclinical infection stimulates the body to produce an acquired resistance in addition to our natural resistance, so that we are better protected from future outside infection; we have, however, no guarantee that our own subclinical infection may not develop into clinical disease later. In short, the first invasion with the tubercle bacillus is a boon if it does not produce progressive primary disease or a later endogenous spread.

This is the whole object of deliberately giving a person a primary infection with BCG. BCG was a bovine tubercle bacillus fifty years ago, but it has long since been rendered non-pathogenic. Introduced as a live vaccine into the skin it multiplies for six weeks and then regresses. Being non-pathogenic, it does not produce progressive primary disease or a later endogenous spread—but it does produce acquired resistance to any subsequent virulent infection.

In BCG we have a valuable preventive weapon—if it is safe and effective. So far one case of lupus of the vaccination site, which rapidly responded to treatment, is the only misadventure reported in this country (Davies, 1955). In the world literature there are 4 cases that have died as the result of BCG vaccination (Irvine, 1957); this is deplorable, but it must be remembered that a total of about 145 million BCG vaccinations have now been carried out in the world, which gives a mortality rate of one in 36 million. Between 1941 and 1949 in England and Wales alone there were 43 deaths from smallpox vaccination (Registrar-General, 1949).

The First (Progress) Report of the Medical Research Council Trial of BCG (1956) gives the answer to the question of its efficacy; it shows that 4 out of 5 of the vaccinated were protected. This was in a group unexposed to known tuberculosis. In an epidemic of tuberculosis in a girls' school in Denmark where the exposure was heavy, 95% of the vaccinated were protected (Hyge, 1947).

If then we accept that BCG vaccine is reasonably safe and that the protection it produces—though not so complete as with smallpox vaccination or diphtheria inoculation—is worth while, why do we not advocate that everyone should be vaccinated? The reason is that, unlike antidiphtheria inoculation, you cannot give BCG to susceptible and immune alike. BCG vaccination in the uninfected person is like smallpox vaccination in slow motion; if BCG is given to someone who has already been infected, the result is very different. An angry reaction begins within a few hours and may reach its height in two days; the site of vaccination rapidly breaks down and the BCG is ejected by the body defences in a profuse purulent discharge. This is known as Koch's phenomenon.

It is wise therefore to differentiate between the infected and uninfected before giving BCG vaccine; fortunately there is a test which will do this—the tuberculin test. Anyone who has been infected with the tubercle bacillus becomes allergic to tuberculin, usually within six weeks. All that is necessary is to apply tuberculin to the skin; if no reaction occurs by the third day he may safely be vaccinated.

There are several methods of applying tuberculin. You may inject it diluted between the layers of the skin (the Mantoux test), scratch it into the skin (the Pirquet test), apply it to the skin under plaster (Moro and jelly tests), or prick it into the skin with needles (the Heaf multiple-puncture test). I shall confine myself to this last and newest test, because in this I think we have the most practical of all the tuberculin tests from the general practitioner's point of view. Let me say at the outset that its main disadvantage is the cost of the Heaf apparatus with which it is given.[1] This carries six needles drawn up behind an end-plate in which there are six holes; on firing the gun the needles stab through the holes in the end-plate to project a set distance. It is sterilized by dipping the end-plate into a shallow tray of spirit and igniting it.

The test is performed by cleaning the skin of the forearm with acetone and placing on it a drop of special tuberculin[2] (PPD 2 mg./ml. in 50% glycerol with 0·5% phenol); this solution is both stable and difficult to contaminate. The drop of tuberculin is spread by the end-plate of the Heaf apparatus into a half-inch circle: the skin of the forearm is drawn taut with the left hand: the end-plate is held firmly in the centre of the tuberculin and the gun fired. No skill is required as the apparatus is mechanically adjusted to perform the same six punctures to the same depth each time (Heaf, 1951).

The test should not be read before the third day and some workers claim that it is reliable even when read as late as the seventh (Townsend and Macdonald, 1955). As with all tuberculin tests, skill is required to read the weaker results. It should be remembered that in most negative reactions the six punctures will still be clearly visible; they may even be surrounded by a ring of erythema and bear a tiny crust in the centre. This should cause no confusion as the criterion of the minimal positive reaction is *palpable induration* around at least four of the punctures. Usually the positive reaction is more definite than this and the six punctures will have coalesced to form a ring or a plaque of induration. If in doubt, call the result negative and retest if possible.

I have discussed this test in some detail because, though it is too new to have reached most textbooks, it is rapidly becoming popular. As a result you may one day be asked to read the result of this test in a 13-year-old kept away from school by illness. Moreover for those of us who can afford this apparatus, a foolproof tuberculin test that is applicable both to the infant and the adult is of great interest.

If a general practitioner is prepared to do a tuberculin test on his patients, should he not be given access to BCG vaccine so that he can vaccinate the negative reactors in his practice? Before answering this question I think I should make it clear that BCG vaccination is nothing like as simple as antidiphtheria inoculation. To begin with it is a live vaccine which should not be used more than fourteen days after manufacture: it comes from Copenhagen and has to be ordered at least two weeks in advance: it deteriorates if not kept in a refrigerator, is damaged by heat and killed by exposure to sunlight; it can contain no preservative and so any ampoule must be used within a short time of opening. The dose is one-tenth of a millilitre, so for accuracy a special long syringe is generally used. The BCG issued by the Ministry has to be injected intracutaneously which requires a special quarter-inch needle with a short bevel and a skill in a technique that few of us were taught in our student days; if the injection is accidentally given subcutaneously, a local abscess the size of a cherry is likely to appear six weeks later. The healthy infant that would be the first care of every family doctor is the greatest BCG headache of all; not only is a baby's

[1]Obtainable from Messrs. Allen & Hanburys Ltd., Bethnal Green, London, E.2, or from Messrs. H. G. East & Co., 37a, Oxford Rd., Cowley, Oxford.

[2]Obtainable as "Protoderm" from Messrs. Allen & Hanburys Ltd., Bethnal Green, London, E.

skin extremely thin and tough, but it is in this age-group that glandular abscesses follow the most perfect vaccinations with distressing frequency.

I feel, therefore, that our generation of general practitioners would be wise to leave BCG vaccination at the moment to specially trained vaccinators. As the number of approved vaccinators is not great—they are mostly chest physicians or school medical officers—they cannot be expected to take on any great extension of BCG vaccination. This is limiting wider use of the vaccine. The solution which I would advocate is that no medical student should in future reach qualification without having had practical training in tuberculin testing and BCG vaccination. Those of our generation who are keen on preventive medicine could also be given practical training in a short postgraduate course. By this means it should soon become possible for the Ministry to release BCG vaccine to the family doctor for use alongside his other preventive inoculations.

Meanwhile we must be prepared to give advice to the mother of the 13-year-old. Before vaccination he will be given an initial tuberculin test: what is the significance of a positive reaction? In a healthy boy this probably only means that he has had a subclinical infection at some time, but this is only a probability; the best way to be sure is to take a chest X-ray. A marked positive reaction is a warning to keep an eye on the boy for some time; the M.R.C. found four times more cases of tuberculosis developing later in fierce reactors than in mild. The fierce reactions are uncomfortable; a dressing of antihistamine ointment is useful.

Next, the negative reactor will be vaccinated with BCG. If a reaction occurs at the site of vaccination in the first week, refer him back to the vaccinator. Little should normally be visible for two weeks when a painless papule appears; this increases to a maximum at six weeks. The average papule measures 10 mm. across; it should not normally exceed 20 mm. Three-quarters of these papules will break down to an ulcer and discharge pus. The average diameter of the ulcer is 5 mm.; it should not normally exceed 10 mm. If a dressing has to be applied to protect the clothing, it should allow as much air to the ulcer as possible; do not occlude it with a plaster dressing or smother it with penicillin ointment. If he wants to go swimming, there is a waterproof rubber sleeve on the market[1] that he can pull over the dressing. If instead of a papule, an abscess the size of a cherry develops, it should be aspirated—not incised; the best plan is to refer it back to the vaccinator.

After the sixth week the vaccination reaction should begin to regress and ulcers should be healed by the tenth week. Large or indolent ulcers may be helped by exposure to sunlight, dusting with PAS or dressing with a special "BCG Reaction Ointment".[2] A painless enlargement of the regional lymph glands normally occurs in 3% of all vaccinations about the sixth week and may last for several weeks; the mother should be reassured and no action taken. Sometimes, however, three to twelve months after vaccination the glands break down to form a cold abscess. This harmless but distressing complication occurs in about 0·5% of infants vaccinated; it is fortunately uncommon in school children. It should be treated by repeated aspiration and replacement of the pus with streptomycin—never by simple incision, or a troublesome sinus may result. There is evidence to suggest that any injection given in the same arm within six months of BCG may precipitate a glandular abscess; for this reason it is wise always to give BCG in the right arm thus leaving the traditional left arm free for other inoculations.

With the possible exception of the very rare complication of lupus, all complications of BCG always heal in the end—even if they have been wrongly treated. You may with complete confidence continue to reassure both yourself and the anxious mother.

Some six to twelve weeks after vaccination the tuberculin test is repeated; this time it should be positive, showing that infection with BCG has taken place and the vaccination has been effective. This change from negative to positive is called "conversion" and this post-vaccination test is called the "conversion test". For school children in the Oxford Region, the conversion rate to a Heaf test is 99·2%; similar findings have been reported in other parts of the country and there is much discussion about whether conversion testing will be necessary in the future.

At intervals vaccinated persons may be followed up with further tuberculin tests to see that the vaccination is still effective; if the tuberculin test returns again to negative—a process known as "reversion"—the person should be revaccinated. It is impracticable to go to these lengths with unexposed school children, but it is important that the full procedure should be carried out on those who are in continual contact with tuberculosis.

Made by Messrs. Kleinerts, 91, New Bond Street, London, W.1.

Glaxo Laboratories make a BCG Reaction Ointment (L.C.C. formula) containing in each gram hydrocortisone acetate 10 mg. dihydro-streptomycin 5,000 units and isonicotinic acid hydrazide 50 mg.

It has been my part to discuss the most modern addition to the methods of preventing pulmonary tuberculosis—BCG vaccination; I am anxious that I should not give the impression that I consider it to be the whole answer to the problem. It is but one more weapon in our armament against tuberculosis—though, I submit, a most effective one. I would offer just one word of caution when discussing our "new" vaccine with European colleagues; Scandinavia has been using it for thirty years and France for thirty-six.

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Sir Geoffrey Marshall:

Chemotherapy

This is a good time for us as clinicians to take stock of our methods of dealing with patients suffering from tuberculosis. The situation has been changing fundamentally as a result of the introduction of effective chemotherapy. Many more patients are being treated in their own homes, and beds in sanatoria are standing empty; whereas only a few years ago there were long lists of patients awaiting admission. The number of new cases notified annually in England and Wales has fallen only slightly, from 50,000 before the war to about 40,000 now; but the death-rate is only one-third of what it was in 1938. This is heartening, but 8,000 deaths per annum from tuberculosis, most of them preventible, should not give us an excuse for complacence. The pattern of mortality has changed. Prior to the war the highest mortality was in young women; now the bulk of the deaths are in elderly men—those in the sixties and seventies, many of whom have been hit hard by the social changes of the Welfare State.

The fall of the gross mortality must be attributed largely to earlier diagnosis by the widespread use of radiography and to more effective treatment, in the form of chemotherapy which followed the advent of streptomycin in 1948.

Now let us consider how we should deal with various types of case, remembering that management of the patient, his dependants and contacts can never be satisfactory unless a large measure of the responsibility is kept in the hands of the general practitioner. Early diagnosis has been achieved in a great many cases by Mass Radiography. It is a procedure we should encourage, not least for men over 50 years of age. We can reassure the public who have been unduly alarmed by propaganda on the dangers of excessive radiation. There is no assessable risk to the subjects of chest radiography.

The Minimal Lesion

When X-ray films show normal lung fields apart from the presence of one or two discrete rounded opacities of not more than one centimetre in diameter, these are commonly called minimal lesions, and not infrequently these cases are kept under observation by periodical radiography, without treatment. Usually there is no sputum and no indication of toxæmia. The X-ray appearance may improve or it may remain unaltered for a year or more. But at any time you may find a sudden change for the worse. Moreover if swabs from the larynx or juice from the stomach are taken when the lesions are first seen, and if these materials are cultured for ten weeks, tubercle bacilli will be found in about one-fifth of the cases. I believe that we should treat all these patients by chemotherapy as soon as the lesions are found. The drugs penetrate the lesion and eliminate the tubercle bacilli most effectively when the lesions are only a few weeks old. Moreover early treatment would prevent the development of bronchial stenosis, with permanent structural damage to the lungs.

Pleural Effusion

The contemporary treatment for this is chemotherapy and early and thorough aspiration. If fluid recurs it is usual to inject streptomycin into the pleural cavity after each aspiration. Chemotherapy should be continued for twelve months at least in cases of minimal lesion and pleural effusion. Regular review with radiography should be maintained for several years.

In more advanced cases the main lesions are likely to be considerable areas of infiltration in the lungs, together with segmental atelectasis which is characterized by wedge-shaped or linear shadows in the lung fields. The presence of tuberculous cavities may be detectable only by tomography.

In all cases chemotherapy is an essential part of the treatment, and rest is necessary for a variable period of weeks or months. Whether treatment is to be carried out at home or in an institution will depend on individual circumstances. In all cases chemotherapy should be begun at home while awaiting admission to hospital. If the sputum is positive and there are children in the house, the patient should go to hospital. If the presence of a pleural effusion, or of cavitation in the lungs calls for constant observation or strict bed rest, hospital is the place for it. The mother and housewife will never rest with an easy mind in her own home, and she should go away until active disease has been arrested. Other patients may do very well at home, but precautions must be taken against spreading infection. There must be no visits by those susceptible to infection, and effective steps must be taken to sterilize sheets, pillow-cases and handkerchiefs.

With regard to the chemotherapy we have three effective drugs, any two of which may be given simultaneously. These drugs are streptomycin, PAS and Isoniazid. There are others, but they are too toxic for consideration here. It is usual to begin treatment with streptomycin by injection and one of the other two drugs by mouth. We must not give one drug by itself as this leads to the development of resistant strains of tubercle bacilli, with consequent danger to the patient and to the public. On the other hand there is little to be said for the administration of all three drugs at the same time. Give two at a time and give them in effective doses. For an adult we give intramuscular injections of streptomycin sulphate, 1 gram once a day on five to seven days a week. PAS is given by mouth on six days a week, 14 to 20 grams daily in divided doses; and Isoniazid is given by mouth in tablets of 100 mg. two or three times a day on six days a week.

As intramuscular injections are inconvenient when a patient resumes active life, we usually continue treatment with PAS and Isoniazid at that stage, and maintain chemotherapy for twelve months in the first instance, with shorter repeat courses at intervals thereafter.

In patients who are acutely ill, and in those who are intolerant of the drugs, great benefit is to be derived—as has been shown by Dr. L. E. Houghton—from giving preparations of the cortisone group together with the anti-tuberculous drugs.

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HOUGHTON, L. E. (1954) *Lancet*, i, 595.

Sir Clement Price Thomas:

Modern Surgical Treatment

I shall deal with my subject mainly from the point of view of the general principles guiding the form of treatment to be advised, and to indicate, by a consideration of cases treated, the reasons for such decisions.

Surgically speaking, after the beneficial general effects of drug therapy are accepted, the most important factor is the effect of the drugs on the bronchial disease; the healing of the disease in the bronchi produces one of two results, either the opening of the bronchi by the decrease in the thickness of the diseased bronchial mucosa leading to a decrease in the size of the cavity, and in favourable cases, its closure, or it leads to stenosis of the bronchi; this latter resulting from the fibrosis following up the healing of the disease, and the subsequent contraction of the fibrous tissue. Stenosis will only occur when the tuberculous process has involved the musculofibrous wall of the bronchus. These processes I believe to be the main factors in either the healing or blocking of tuberculous cavities. When stenosis affects the larger bronchi such as the lobar or main bronchi, mechanical problems ensue which are not strictly related to the tuberculous disease. One other factor resulting from the healing of tuberculous bronchial disease is that resection of the lung becomes a safer procedure in that the line of section of the bronchus will then be through healthy tissue.

There is a tendency to consider resection and relaxation operations as competitive procedures, instead of considering them as being complementary. As I shall show later, as a broad differentiation, resection should be reserved for tuberculous lesions which are either non-cavitated or have been converted from open lesions to closed lesions or, at least, into lesions which have ceased shedding tubercle bacilli, as judged by direct smears or cultures; on the other hand, open cavitated lesions, with a positive sputum, still are

best treated by thoracoplasty, if the cavity be in such a position that closure can be anticipated.

The practical politics of the issue are as have been indicated by my colleagues. All patients, after a satisfactory diagnosis has been made on all three grounds, clinical, radiological and bacteriological (including the sensitivity of the organisms to the available drugs), should be started on chemotherapy, using always two of the available drugs, never one, in order to prevent the emergency of insensitive strains of bacilli. It is usual to use streptomycin as one of them at the outset. The length of treatment will depend on many factors: the extent and severity of the disease, the persistence or otherwise of a positive sputum, the closure or blocking of the cavities; but, generally speaking, treatment should be continued for as long as there is steady even progress, on clinical, radiological and bacteriological grounds. No patient, who has a positive sputum at the outset of the disease, should be submitted to resection before he has had at least three months' medical treatment, and in those with cavitation, a minimum of six months' pre-operative treatment is safer.

Admittedly other factors arise which may modify the above course, but it should be quite fully realized that to modify such a curriculum is to increase the potential risk to the patient.

The tables list a series of cases submitted to resection for pulmonary tuberculosis and personally operated upon.

TABLE I

Total No. of cases	366
Total deaths	28 (7·65%)
Early	18 (4·9%)
Late	10 (2·7%)

TABLE II

		Deaths	
Cavitation I	53	8	early 6 (11·3%) late 2
Cavitation II	93	3	early 0 late 3
Solid	131	2	early 0 late 2
Cav. Sol.	22	0	

Cavitation I means that open cavitation was present at the time of operation.

Cavitation II indicates that a cavity was present when the patient first came under observation, but was closed at the time of operation.

Solid is self-explanatory.

Cav. sol. indicates a solid lesion showing evidence of cavitation.

Table I shows the number of cases with the early and late mortality. It is noteworthy that there has been only one early death in the last three years and that from coronary thrombosis.

From Tables II and III, it will be seen that all of the 18 early deaths, with the one exception already referred to who had a solid lesion, occurred in patients who had open cavitated disease at the time of operation. By early death is meant those patients who died whilst in hospital, who were, in fact, never fit enough to leave. Some died quite some time post-operatively from some complication of the operation, most commonly bronchial fistula with a complicating empyema and spread of the disease.

As would be expected, the highest mortality accompanies the more complicated forms of the disease, empyema and stenosis with underlying open cavitated disease. Interestingly enough, destroyed lungs have a lower operative mortality than the former two, and this I believe to be due to the fact that in quite an appreciable number of this latter group the tuberculous disease has burnt itself out. In other words, the patient has conquered the tuberculous infection at the expense of gross anatomical destruction.

If the whole group of patients with cavitated disease be alone considered, 85 in all, 17 patients died in hospital, a mortality rate of 20%.

This high mortality rate was, without doubt, due to operating on patients with open cavitated disease and a positive sputum at a time when the necessity for prolonged pre-operative chemotherapy in such cases was not properly appreciated. I believe that the time-duration of such treatment, with adequate daily dosage, is of more significance than the total quantitative dosage. There can be no question that the whole success of surgical intervention, especially resection, depends on adequate and effective pre-operative treatment.

TABLE III

		Deaths
Stenosis Total No.	22	4 (18·18%)
Without cav.	15	0
With cav.	7	4 { early 4 (57·1%) late 0
Empyema Total No.	28	7 (25 %)
Without cav.	20	2 { early 1 (5%) late 1
With cav.	8	5 { early 4 (50%) late 1
Destroyed lung	17	4 { early 3 (17·6%) late 1

TABLE IV

Segmental Resections. Total No. 194

Deaths Total No. 6

Early .. .. 4 (2·06%)

Late 2

		Deaths
Cavitation I	7	2 { early 2 (28·5%) late 0
Cavitation II	61	2 { early 0 late 2
Solid	100	0
Cav. sol.	14	0
Empyema	10	1 { early 1 (10%) late 0
Stenosis	2	1 { early 1 (50%) late 0

TABLE V

Lobectomy. Total No. 107

Deaths. Total No. 8

Early .. .. .. 2 (1·86%)

Late 6

		Deaths
Cavitation I	30	4 { early 2 (6·6%) late 2
Cavitation II	29	1 { early 0 late 1
Solid	29	2 { early 0 late 2
Cav. sol.	6	0
Empyema	7	1 { early 0 late 1
Stenosis	6	0

TABLE VI

Pneumonectomy. Total No. .. 65

Deaths. Total No. 14

Early .. .. 12(18·46%)

Late 2

		Deaths
Cavitation I	16	2 { early 2 (12·5%) late 0
Cavitation II	2	0
Solid	2	0
Cav. sol.	2	0
Empyema	11	5 { early 4 (36·3%) late 1
Stenosis	15	3 { early 3 (20%) late 0
Destroyed	17	4 { early 3 (17·6%) late 1

In a certain number of patients, cavity closure and sputum conversion do not occur even with prolonged treatment, due commonly to drug resistance of the organisms; then again adequate treatment cannot be given owing to the patient's sensitivity to the drugs—in one case, the patient developed agranulocytosis. In any case, whatever the cause of failure, in such cases, if there is a reasonable chance of cavity closure, thoracoplasty is far and away the safer procedure. If the cavity, however, is in such a place as to preclude reasonable expectation of closure, for example in the basic segments of the lower lobe or in the middle lobe, then the risk may have to be undertaken but the risk should be clearly recognized.

It will be agreed that the aim in view is the cure of the patient's disease with as little risk as possible, and the choice of treatment lies in the accurate assessment of these two factors.

Tables IV, V and VI list the types of operative intervention and demonstrate the same points relative to open cavitated disease, and that the mortality is greater in proportion to the extent of the intervention.

The end-results of resection cannot yet be accurately assessed. It will be seen that there are 10 late deaths, this giving a mortality of 2·8% in the 348 who survive after leaving hospital, and of these, about two-thirds die of a disease other than tuberculosis. The end-results are difficult to report owing to the short time available since resection became general (with four exceptions, the longest survival is eight years); and also to the inadequate follow-up at the time of reporting. At the time of writing, however, of those followed up about 3% are classified as being poor, about 84% as good, and about 13% as fair. I feel reasonably certain that in the latter two groups, the majority of those considered fair, in due course, will eventually merge into those considered to be good.

I suggest that the conclusions to be drawn from the foregoing experience are that resection of the lung for tuberculosis can be rendered a safer procedure, provided adequate and effective chemotherapy is carried out before operation is undertaken, and that more than probably it will be attended by good long-term results.

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Section of Medicine

President—G. E. BEAUMONT, M.A., D.M., F.R.C.P., D.P.H.

[*January* 22, 1957]

DISCUSSION ON ANURIA IN MEDICAL CONDITIONS

Dr. M. D. Milne:

Anuria, which is strictly defined as *complete* failure of urine formation, is rare. Complete anuria is much more likely in surgical conditions associated with obstruction of both ureters or of the ureter of a single kidney. The term "anuria" is, however, often inaccurately applied to conditions associated with severe oliguria in which the daily urine volume is insufficient to maintain normal kidney function and preserve biochemical homeostasis. A better and more accurate term is "acute oliguric renal failure".

The daily urinary volume (v) is related to the mean urinary concentration and the total amount of solute excreted daily. Urinary concentration is dependent on the fluid intake and on the amount of water loss by extra-renal channels, e.g. the stools, sweat, and expired air. Solute excretion is mainly influenced by the diet, being high with a salty and high-protein diet and low with a diet containing little salt and protein. Normally, the following mathematical relationship holds (Fig. 1):

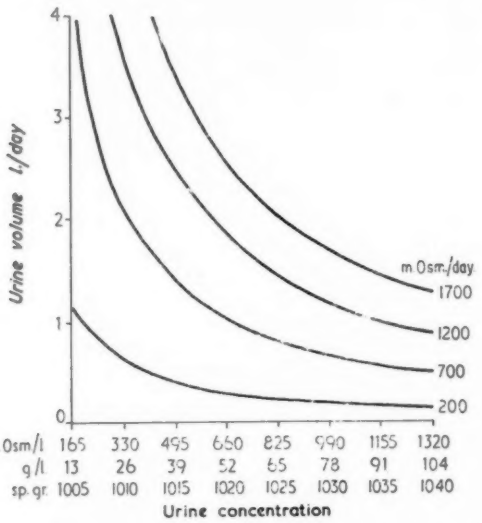


FIG. 1.—Relationship between urinary concentration and urine volume for (*a*) electrolyte-free and protein-free diet (200 m.osmoles/day). (*b*) Low protein diet (700 m.osmoles/day). (*c*) Good normal diet (1,200 m.osmoles/day). (*d*) High protein diet (1,700 m.osmoles/day). The urine volume is dependent on the amount of solute excretion as well as on the concentration of the urine. With low solute excretion satisfactory renal function is compatible with moderate oliguria. Urinary concentration is best expressed in m.osmoles/l., but may also be expressed in grams/l. and as urinary specific gravity. Equivalents between these values are only approximate.

$$c \times v = s$$

where c is the mean urinary concentration in m.osmoles/ml., v is the urine volume in ml./day, and s is the solute required to be excreted in m.osmoles/day. In clinical practice urinary concentration is measured by determination of specific gravity rather than the more accurate but more difficult method of estimation of urinary osmolarity. Approximate equivalent values are given in the abscissa of Fig. 1.

If a patient is receiving a protein and electrolyte free diet, e.g. in parenteral feeding with 5% glucose, the amount of solute excreted is entirely derived from the metabolic breakdown of body protein and may be less than 300 m.osmoles/day. Should the patient be dehydrated from vomiting or diarrhœa, a concentrated urine of an osmolarity greater than 1 m.osmole/ml. may be excreted. In such circumstances the daily urine volume would be only 300 ml./day, but there would be no renal failure and no increase of blood urea or non-protein nitrogen. This type of oliguria is physiological and obviously should not be classed as acute renal failure.

Acute oliguric renal failure is always associated with uræmia which steadily deteriorates unless diuresis occurs or the patient is treated by dialysis methods, e.g. the artificial kidney. In contrast, in chronic renal failure with polyuria, the degree of uræmia may remain unchanged for many months or even years. Acute renal failure may occur in patients with previously normal kidneys or in patients with preceding renal disease. The prognosis is obviously worse in the latter group, since at best, renal function can only be restored to its original impaired state. Differential diagnosis in patients seen for the first time in acute renal failure may be difficult. The single most useful feature is that the patients with an acute exacerbation of previous chronic uræmia have a normochromic anæmia due to long-standing renal disease. The two most important causes of oliguria in chronic uræmia are salt depletion or an acute exacerbation of chronic pyelonephritis. Severe salt depletion is particularly liable to occur in uræmic patients from vomiting or diarrhœa. If salt depletion occurs in normal subjects the kidneys will compensate by secretion of a salt-free urine due to increased aldosterone production. This cannot occur in uræmic patients as the renal tubules can no longer retain sodium efficiently, and continued salt loss occurs both in gastro-intestinal fluids and in the urine. Recognition of these two causes is of great importance since effective therapy by saline infusions or by antibiotics may lead to rapid improvement. If, however, these two factors can be excluded, the prognosis of an acute exacerbation of chronic uræmia is extremely grave since it is usually due to almost complete destruction of existing glomerular function by the previous renal disease.

The most important cause of acute renal failure in previously healthy patients is renal ischæmia. Classification is best based on the anatomical site of underlying disease:

(*a*) Obstruction of the main renal arteries.
(*b*) Obstruction of renal veins.
(*c*) Obstruction of smaller renal arteries or of the afferent glomerular arterioles.
(*d*) Glomerular lesions.
(*e*) Acute renal circulatory failure.
(*f*) Acute tubular necrosis.
(*g*) Renal cortical necrosis.
(*h*) Proximal tubular necrosis.
(*i*) Renal papillary necrosis.
(*j*) Obstructive lesions of the ureters.

Obstruction of the main renal arteries.—This may occur as a result of embolus, thrombosis, or a dissecting aneurysm of the abdominal aorta involving the origins of the renal arteries, and is obviously more liable to occur in a patient with a single kidney. The commonest cause of pathology at this site is, however, diagnostic aortography. This is a potentially dangerous investigation and should only be performed if the information obtained will be of direct value to the patient. Anuria may result from renal artery thrombosis, intimal stripping by injection of contrast media directly into the aortic wall (Gaylis and Laws, 1956), or from acute tubular necrosis from local high concentration of diodone. Miller *et al.* (1954) report 4 cases all of whom recovered, and Alwall *et al.* (1955) describe 8 cases with 2 deaths. I have recently seen 3 cases of which 1 died. The use of the Seldinger technique (1953) avoids the danger of intimal stripping but anuria may still occur from the other two causes. The technique is especially dangerous if only a single kidney is present.

Obstruction of the main renal veins.—This will cause anuria if the obstruction is complete. Renal vein thrombosis may or may not be associated with thrombosis of the inferior vena cava (Harrison *et al.*, 1956). Primary renal vein thrombosis is especially liable to occur

as a complication of acute gastro-enteritis in the first few months of life. Renal vein thrombosis in adults is more usually secondary to chronic renal disease with gross reduction of renal blood flow and is especially likely to occur in cases of secondary renal amyloidosis (Vilk, 1940; Harrison *et al.*, 1956). This type of anuria is also more liable to occur in patients with only a single kidney.

Obstruction of the smaller renal arteries.—The smaller renal arteries may be involved in polyarteritis nodosa, the kidneys being the organs most commonly affected. The uræmia usually terminates in an oliguric phase. Polyarteritis should be suspected if there is evidence of arteritis elsewhere and if there is rapid deterioration of renal function in patients in whom the blood pressure is normal or only slightly increased. Usually chronic renal failure without rise of blood pressure is only slowly progressive but cases of polyarteritis are exceptional, and there is rapid renal functional and structural damage. In

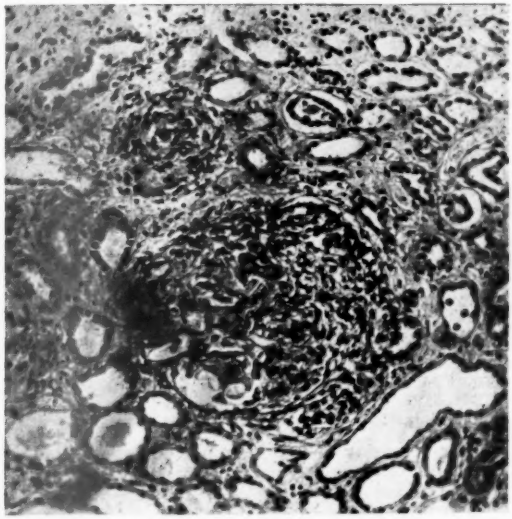


FIG. 2.—Section of glomerulus in a case of polyarteritis nodosa with severe and fatal oliguria. There is widespread necrotizing arteriolitis of the afferent glomerular arterioles. Hæmalum and eosin. ×142.

some cases the afferent glomerular arterioles are especially involved (Fig. 2), but necrotizing arteriolitis in this location may also occur in other types of renal disease, e.g. acute glomerulonephritis or malignant hypertension. Treatment with cortisone will often prevent further activity elsewhere, but unfortunately has little if any beneficial effect on the renal lesion. An accurate post-mortem diagnosis is often more difficult after cortisone therapy.

Glomerular lesions.—In a small proportion of cases of acute glomerular nephritis the oliguria may be severe enough to cause acute renal failure. Many cases show complete anuria and the prognosis is worse than in the more common acute tubular necrosis. The diagnosis is made by finding other signs of acute nephritis such as œdema and hypertension. Severe oliguria and rapidly progressive uræmia may occur in the subacute stage of glomerulonephritis, and is not uncommon in the nephropathy of Henoch-Schönlein purpura.

Acute renal circulatory failure and acute tubular necrosis.—This type of oliguria is secondary to conditions involving hæmorrhage and shock and is therefore more common in obstetric or surgical practice than in medical cases. In acute renal circulatory failure diuresis occurs when the circulatory insufficiency is effectively treated, but in acute tubular necrosis oliguria persists for a varying period up to two or three weeks. Since there is no permanent glomerular change the prognosis is good and there are no sequelæ if the patient survives. In purely medical practice, common causes are coronary thrombosis, gastro-intestinal hæmorrhage, incompatible blood transfusion, acute hæmolysis as in blackwater fever, and circulatory collapse from overdosage with ganglionic blocking drugs.

Renal cortical necrosis affects both glomeruli and tubules. About 80% of cases of renal cortical necrosis occur in association with concealed accidental hæmorrhage of pregnancy.

The remaining cases may occur either in children or adults and have usually been associated with episodes of severe vomiting or diarrhœa or with septicæmia or bacteræmia. Complete cortical necrosis is obviously inevitably fatal, but in less severe cases with only partial necrosis the patient may recover. There is, however, some permanent reduction of renal function owing to patchy destruction of glomeruli.

Proximal tubular necrosis follows ingestion of nephrotoxic drugs and poisons, e.g. mercuric chloride, potassium bichromate, chlorates, carbon tetrachloride, and large doses of sulphonamide drugs. There is widespread necrosis of proximal tubular cells without rupture of the basal membrane. The course and prognosis is similar to that of acute tubular necrosis.

Renal papillary necrosis.—In this condition there is necrosis of some or all of the renal papillæ (Fig. 3). About two-thirds of cases occur in diabetic patients with secondary

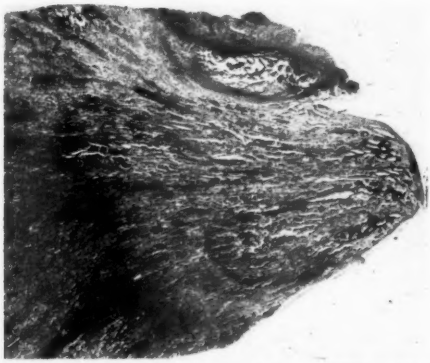


FIG. 3.—Section of renal papilla in a case of necrotizing papillitis with severe and fatal oliguria. There is complete necrosis of almost the whole papilla. A hæmorrhagic area separates the area of necrosis from living kidney tissue. Hæmalum and eosin. ×6.

pyelonephritis. The oliguria usually follows an acute exacerbation of urinary infection with severe dysuria, pyrexia and hæmaturia. There may be renal colic due to fragments of necrosed papillæ being passed down the ureters.

Ureteric obstruction.—This is a surgical variety of acute uræmia but may closely simulate the medical conditions already described. Anuria is usually complete and is obviously more likely to occur if there is a single kidney.

Conservative management by a protein and electrolyte-free but high caloric diet together with fluid restriction is the basis of treatment in all cases of acute renal failure. Blood urea, and serum potassium and bicarbonate should be determined each day. Treatment should be supplemented by dialysis, preferably by the artificial kidney, if any of the following signs of failure of conservative measures are found:

(*a*) Serum potassium above 8 mEq./1.
(*b*) Serum bicarbonate below 10 mEq./1.
(*c*) Electrocardiographic evidence of progressive hyperkalæmia, acidotic breathing, deepening stupor, or uræmic twitching or hyperexcitability.

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Dr. A. M. Joekes:

The importance of the recognition of the presence or onset of acute renal failure was stressed. The recognition is made both earlier and more certainly by observing the volume and quality of the urine passed than from biochemical changes in the blood. Oliguria was defined as a urine volume less than 700 ml./twenty-four hours. In the presence of severe renal failure the specific gravity will lie between 1008 and 1014. With good renal function a twenty-four-hour urine volume of 700 ml. or less will result in a specific gravity

of 1018 or higher. In the absence of glycosuria or heavy proteinuria a specific gravity exceeding 1018 can be accepted as evidence of good renal function. Spurious low specific gravity oliguria may be met with under circumstances in which a low nitrogen intake is maintained and sodium chloride retention by the kidney is occurring. As a working rule it may be taken that the urine in a low specific gravity oliguria with severe renal damage will always contain considerable amounts of sodium and chloride and that their absence implies a physiological response by the kidney.

Among several illustrative cases of acute tubular necrosis complicating medical conditions, were included four occurring during the course of non-fatal hepatic disturbances in which no surgical intervention had occurred in the immediate past; in all 4 patients the acute renal failure ran the typical course of an acute tubular necrosis with recovery.

The only illustrative case which is here recorded is that of a young man of 21 in whom an acute tubular necrosis followed a severe hypotensive episode after a large pulmonary embolus.

History.—Male, aged 21.

Admitted to hospital 18.8.56 with a short history of cold, some pain in the left lower chest and blood-flecked sputum. On admission, an afebrile, healthy-looking boy. B.P. 110/65 with the only physical signs being some diminished movement of the left chest.

The following day he became febrile and the next day a small left-sided pleural effusion was discovered which contained a straw-coloured fluid. Mantoux 1/10,000 positive, W.B.C. 9,000, E.S.R. 86 mm. in the first hour. 21.8.56: Episode of pain in the right chest. 22.8.56: Small R pleural effusion.

Presumptive diagnosis—pulmonary tuberculosis and treatment started with streptomycin and isoniazid.

1.9.56: After swinging legs over the side of the bed suddenly collapsed and was found pulseless and unconscious at 7 a.m. Some two hours later intravenous infusion containing noradrenaline was started with rapid improvement in the general condition. B.P. which had previously slowly risen to 75/55 rose to 104/75. Noradrenaline drip was maintained for the following twenty-four hours, the B.P. at times still dropping as low as 85/60.

From the time of the sudden collapse, the patient was severely oliguric for four days. On the fifth, the urine volume started to increase and the urine volume reached one litre in the twenty-four hours on the seventh day. The blood urea, urine volume and body-weight are shown in Fig. 1. The course of the renal failure was typical of an acute tubular necrosis.

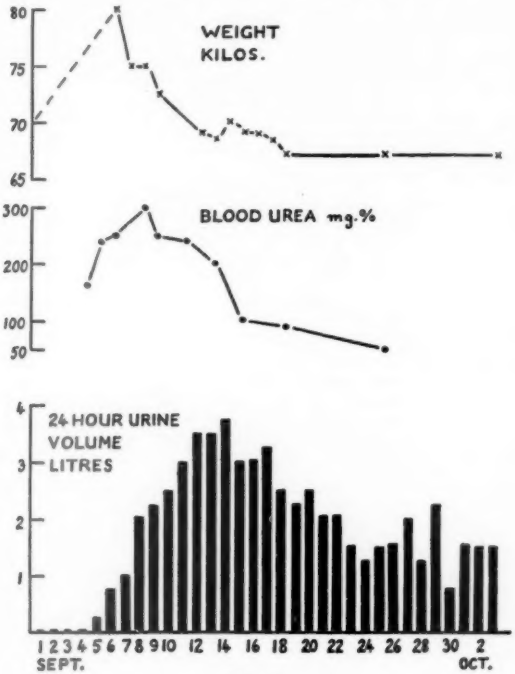


FIG. 1.

The pulmonary condition prior to the hypotensive episode was, in retrospect, typical of multiple pulmonary emboli, with a massive one occurring on 1.9.56. The radiological appearances of the lungs were characteristic and slight œdema of the ankle and calf tenderness were present on 7.9.56. ECG showed very severe acute right ventricular strain at this time.

During the first three days after the massive pulmonary embolus on 1.9.56, the patient was fairly severely overhydrated and on 4.9.56 the patient weighed 10 kg. more than his normal weight. At this time, he was overbreathing quite out of proportion to his chemical acidosis; this was assumed to be consistent with the hyperpnœa typically seen with pulmonary embolus. In view of the severe overhydration and the absence of a marked rise in serum potassium, the patient was left without any fluid administration for twenty-four hours in the hope that he would lose water via the lungs. This was most strikingly successful, the weight falling from 80 to 75 kg. in thirty-six hours, with marked improvement in his general condition. From then he was managed on intravenous alimentation, with 40% glucose and insulin (1 unit to 4 grams glucose) added to the drip. During the early diuretic phase, sodium and potassium loss in the urine was replaced intravenously.

The recovery was complicated by a severe penicillin skin rash, but renal function steadily improved, and he returned to full work three months after the initial illness.

Dr. E. M. Darmady:

The Renal Changes in Anuria Following Medical Conditions

Anuria follows a very large number of ætiological factors, but more frequently shock, disturbances of the electrolyte water balance, intravascular hæmolysis or combinations of all these factors. It is fortunate that the pathological changes in the kidney are similar, even to the extent that it is not possible to determine from the microscopical examinations the nature of the ætiological agent. This syndrome is known as acute tubular necrosis, and I propose to confine my remarks entirely to this condition.

This report is based on the examination of 53 kidneys obtained from post-mortem, and sent to us by many colleagues to whom we are grateful. In addition, we have examined five that have followed a specific nephrotoxin. Oliver, MacDowell and Tracey (1951) and Dible (1953) have already shown that the pathological changes differ from those seen in acute tubular necrosis, but as we have examined so few cases following nephrotoxins we do not propose to discuss them here.

All the kidneys have been examined both by microdissection and histological means. We have arranged them according to the duration and stage of their illness, and in order that the pathological changes can be correlated with the urinary output. Four phases are usually recognized: (1) Onset; (2) Anuric or oliguric; (3) Diuretic; (4) Late diuretic; and we propose to describe our findings in each phase:

(1) *Onset phase.*—In the onset phase, there is no anatomical defect in the nephron, although the glomerulus is often engorged with blood. Histological preparations using standard staining methods seldom suggest there are changes in the tubules, but by microdissection many nephrons show focal areas of epithelial disorganization, and loss of translucency. This is by no means widespread, and may be localized to a specific nephron. Staining for alkaline phosphatase confirms the early changes in the proximal tubules, for in many areas alkaline phosphatase is absent. At this stage the proximal tubules are most affected, although many nephrons may show little or no change. This is of importance, and will be referred to later.

(2) *Anuric and oliguric phase.*—The changes of the onset phase gradually merge into the findings of this stage. Transparent casts start to appear in the lower end of the proximal tubule, and later in the loops of Henle. By microdissection the focal epithelial changes in the proximal tubule become more marked, and there is shrinkage of the epithelium so that the lumen is now apparent. Once again many nephrons may be considered normal, although the volume of urine passed in life may be small. The epithelium soon starts to regenerate, and heaping of the cells may be observed. In some areas, necrosis of the cells may be apparent, and the lower part of the nephron may be dilated even though casts are not present.

About the fourth to sixth day after onset, the distal tubule begins to show widespread epithelial degeneration, while casts of all types start to appear in the lower part of the nephron affecting the loops of Henle, and the distal and collecting tubules. The lumen is dilated since the epithelium is shrunken and flattened. At the same time, rupture in the wall of the tubule appear and are found in all parts of the nephron. These probably correspond to tubulo-venous and tubulo-interstitial ruptures described by Dunn, Gillespie and Niven (1941), and Bywaters and Dible (1942).

The ruptures in the interstitial tissue are accompanied by a brisk lymphocytic reaction, particularly where the protein-like material had leaked into the tissues. The appearance of casts seen by microdissection are interesting in that they often affect the same nephron.

The casts seem to take up the shape of the lumen and epithelium arrangement, and are frequently multiple. At the same time the tubule is not dilated either at the site of the cast or above the cast, unless the tubule wall has ruptured. The presence of casts and the outstanding damage to the distal tubules at this stage of the disease has given rise to the misnomer "lower nephron nephrosis". As it is at this stage the untreated case usually dies early pathologists were obviously impressed by the extent of the lesion of the lower nephron (Lucke, 1946).

(3) *Diuretic phase.*—No hard and fast rules can be laid down as to the changes found in the early diuretic phase, for the histologist cannot from histological grounds alone predict whether at the time of death or biopsy, the patient was in anuria or diuresis. However, in general, evidence of regeneration is apparent in all parts of the nephron. The epithelium of the proximal tubule is usually shrunken and flattened, and by histological standards now begins to show a more regular pattern, whilst nuclei show mitotic divisions. As the period of time after the onset lengthens, so the repair of the nephron continues, starting from the proximal tubule downwards. Indeed, not only does the epithelium recover, but the casts, particularly in the collecting tubules show polymorphic nuclear leucocytic and macrophage infiltration.

Discussion

Although the sequence of renal changes is well recognized, there are these points in the understanding of the syndrome that require further elucidation. First, interstitial œdema that may be found particularly in the early anuric phase, or in the early diuretic phase. Second, the random distribution of the lesions, and third, the mechanism of the anuria.

As regards the first, Dible (1953) has suggested that the interstitial œdema which is often found in the boundary zone may result in "relative functional bar" to the passage of the filtrate, and this may maintain the anuria or oliguria, and at the same time it has often been suggested that there is a rise in intra-renal pressure. From microdissection studies, there is no evidence to confirm this, for the tubules show no evidence of collapse or dilatation higher in the nephron which would result from such an obstruction. Indeed, de Wardener (1955), who measured the intra-renal pressure following experimental acute tubular necrosis, found that the pressure was unaltered. For this reason, together with the fact that the interstitial œdema is not found constantly, we suggest that this view is untenable.

With regard to the second point, both histological and microdissection studies confirm the random distribution of the lesions. Indeed many nephrons may show little or no damage, whilst others are so damaged by rupture of the wall and cast formation that it is unlikely that they could have ever recovered function. Conversely, the lesions, even though not seriously disturbing the epithelium pattern, do not appear sufficient to prevent complete urinary function. In other renal conditions, epithelium disarrangement of the same severity has not been associated in life with oliguria. Furthermore, it is clear that in the early stages of the disease the tubular damage is not sufficient to prevent the passage of the filtrate. This makes us believe that the cause of the anuria cannot be directly attributed to the lesions of the tubules, but rather to the function of the glomerulus.

On the third point, it is possible that the findings following the anuria of the homotransplanted kidney may shed light on the mechanism of the anuria in this syndrome. Following homotransplantation of the kidney in dogs, urine is usually secreted for about four to six days after transplantation. At about this time there is an abrupt cessation of urine flow. Examination of the nephron at this time shows the glomerular neck to be narrowed and devoid of epithelium, but as these changes are also found before the cessation of urine flow, it is clearly not directly responsible for the anuria (Darmady, Dempster and Straack, 1955). Injection of indian ink in the renal circulation at the time of the anuria shows the glomeruli to be engorged with blood. Furthermore, cortisone treatment assists in preventing the changes in the glomerular neck, but it does not prevent the onset of anuria, and kidneys examined at this stage show a similar overfilling of the glomeruli. This suggests to us that the blood flow through the glomerulus is stagnant or sluggish, and that the tone of the glomerular tuft has been lost. The congestion of the glomerulus in the onset phase of acute tubular necrosis has led us to believe that the mechanism of the anuria is similar, and that the cause should be sought in the glomerulus.

Finally, it is often noted in the recovery or diuretic phase, there may be considerable excess urinary potassium. In primary aldosteronism, of which we have had the opportunity of examining 5 cases, vacuolation of the epthelium, particularly of the proximal tubule, is seen. Similar changes can also be found in some cases in the diuretic phase, which suggests that the potassium depletion may be a significant factor.

SUMMARY

(1) The renal changes in acute tubular necrosis in cases have been traced through the natural history of the syndrome, by both microdissection and histological preparations.

(2) The random distribution of the lesions is stressed.

(3) The role of glomerulus in producing anuria is discussed.

(4) The presence of vacuolation in the tubular epithelium of patients dying in the diuretic phase is analogous to the changes found in 5 cases of primary aldosteronism.

My thanks are due to Miss F. Stranack who has painstakingly prepared so many tissues for examination, and to the Medical Research Council for an expenses grant, which has made this work possible. I am also grateful to my many colleagues, who have provided the material on which these observations have been based.

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[*February* 26, 1957]

DISCUSSION ON THE PHARMACOLOGICAL AND MEDICAL ASPECTS OF SMOKING

Professor J. H. Burn (Department of Pharmacology, Oxford University): *The Pharmacology of Smoking*

Amounts of nicotine received in smoking.—The observation that nicotine stimulates sympathetic ganglia is now an old one, and most people remember that the stimulant action passes over to a paralysing action when nicotine is applied. In the amounts which normally reach man, however, it is a ganglionic stimulant. I would like to begin my remarks with a consideration of this very point. How much nicotine does a man smoking a cigarette take in? There have been some surprising estimates, which seem to me too high. Thus Haag and Larson (1944) have concluded that cigarette smokers who inhale retain about 3 mg. nicotine from each cigarette, while those who do not inhale retain 0·35 mg. Now observations made in my own department by Ling and Wynn Parry (1949) suggested that the amounts were much smaller. They set up a long glass U-tube each arm of which was 50 cm. long and of internal diameter 1 cm. The U-tube was immersed in running cold water. To one side of the U-tube a holder was attached in which a cigarette could be fixed, and the other side was attached to a 50 ml. flask which was in turn attached to a filter pump which applied weak suction. A T-piece near the pump could be opened or closed so as to allow suction to draw air through the cigarette at intervals similar to those used by a smoker in smoking a cigarette. Usually 5 cigarettes were "smoked" in succession, and the nicotine condensed in the U-tube and in the flask was then collected and estimated. The deposit was dissolved in weak acid, made alkaline and extracted with ether. The ether extract was allowed to dry and the nicotine was taken up in 1% tartaric acid. It was then estimated on the blood pressure of a spinal cat. Results were obtained by Ling in 1935 and by Wynn Parry in 1948. They showed that the amount of nicotine entering the mouth during the smoking of one cigarette, which contains 1 gram tobacco, is between 0·6 mg. and 1·0 mg. The cigarettes used were the brands commonly smoked in Britain, including Players, Gold Flake and State Express.

This result gains confirmation from observations published by Burn *et al.* (1945) on the antidiuretic action of nicotine. Thus one subject who drank 1 litre of warm water and measured its rate of excretion by emptying his bladder at 15 min. intervals, smoked one cigarette, inhaling deeply, 45 min. after drinking the water. This caused inhibition of the diuresis for over one hour, the interval between the maximum rate of excretion before and after smoking being 105 min. On another occasion he repeated the experiment, but instead of smoking a cigarette, he received an injection of 1 mg. nicotine acid tartrate, corresponding to 0·33 mg. nicotine calculated as base. This produced a longer

inhibition of diuresis, the interval between the maximum rate of excretion before and after receiving the injection being 150 min. This, and a similar result in a second subject, suggested that the amount of nicotine reaching the blood when a subject inhales deeply is about 0·3 mg. per cigarette, and probably only one-third of the amount entering the mouth. Thus the figures given for the amounts of nicotine in the smoke of cigarettes by Haag and Larson (1944) and by Wolman (1953) do not apply to cigarettes obtained in Britain. Our lower results may be due to the use of the biological method for estimating nicotine, which ignores related substances which are without physiological action.

Heart-rate and blood pressure.—That smoking raises the heart-rate and the blood pressure is generally agreed. The rise in heart-rate is to be expected from the stimulation of the stellate ganglia by the nicotine. This would lead to a discharge of impulses along the cardio-accelerator nerves. The rise in blood pressure is also to be expected from the stimulation of the sympathetic ganglia, and, like the rise in heart-rate it may also be due in part to a release of adrenaline and noradrenaline from the adrenal medulla. In normal subjects the rise of blood pressure was found by Roth *et al.* (1944) to be about 10 to 20 mm., but it was found to be greater in patients with hypertension (Roth, 1954). In 16 patients whose average blood pressure was 170/117, the average increase caused was 38 mm. systolic and 23 mm. diastolic; 2 cigarettes were smoked in both series.

Peripheral vasoconstriction.—The rise of blood pressure is due, in the main, to vasoconstriction and the vasoconstriction is prominent in the vessels of the skin. Lampson (1935) used a plethysmographic method of measuring the rate of blood flow through the hand, and observed a striking fall in the blood flow when the subject smoked and inhaled a cigarette. The hand was in water at 32° C., and the flow per 100 ml. of hand fell from 19 to 4 ml. per min.

Other observers have recorded changes in skin temperature. Among these have been Barker (1931), Wright (1933), Wright and Moffatt (1934), Maddock *et al.* (1936) and Roth (1951). An example of the observations made showed a fall in the surface temperature at the finger tips from 32·5° C. to 25·8° C., the temperature returning to 32·4° C. about 35 min. after the end of smoking.

The explanation of these effects which would naturally be put forward is that the nicotine stimulated the ganglia of the sympathetic chain and so caused the vasoconstriction. It is, however, not certain that the action of the nicotine is only or mainly on the sympathetic chain. In the first place, observations on the perfused vessels of an isolated organ indicate that nicotine has a peripheral constrictor action in addition to its ordinary ganglionic action. This effect was first demonstrated with small doses (5 μg.) of nicotine by Haimovici and Pick (1946) in the perfused vessels of the frog. My colleague Kottegoda (1953*a*) observed a similar effect in the perfused rabbit ear and saw that it was abolished by hexamethonium. This seemed to indicate that nicotine was not acting directly on the vessels, but on some ganglion-like structure, though none was known in the tissues of the ear. Kottegoda also showed that the effect of nicotine was reversed when the vessels were perfused with a solution containing priscol. Now, in the presence of priscol, the constrictor action of adrenaline is reversed to a dilator action, and so it appeared that the constriction caused by nicotine might be due to the release of adrenaline, because the constrictor effect of nicotine was reversed in the presence of priscol. Finally, Ginzel and Kottegoda (1953) made observations on the isolated ears of rabbits in which the sympathetic fibres had degenerated. They removed the superior cervical ganglion and the stellate ganglion on one side, and three weeks later they tested such denervated ears. The action of nicotine was unaltered. In small amounts, e.g. 5 μg., it caused a vasoconstriction which was blocked by hexamethonium, and which was reversed to a vasodilator action in the presence of priscol.

The mechanism of the effect of nicotine is obscure. The effect is clearly independent of the postganglionic sympathetic fibres. Perhaps there is chromaffin tissue surrounding the small vessels of the ear; this tissue, which is present in various parts of the body, contains noradrenaline with a small amount of adrenaline. The action of nicotine may be to release these amines.

These observations may very well have an importance for human skin, particularly in diseases such as thrombo-angiitis obliterans and Raynaud's disease. It appears to be established that smoking may bring on the ulcers and the gangrene which is characteristic of thrombo-angiitis obliterans, and that the condition heals when smoking stops. McDevitt and Wright (1955) quote several cases where the disease was sufficiently severe that an amputation of a limb was required, and where a connexion with smoking was established by a recurrence of attacks when smoking was resumed. One was of a middle-aged

physician who had thrombo-angiitis for five years. He had three severe attacks, each associated with the resumption of smoking.

Another was a patient in the New York Hospital who first had active thrombo-angiitis in 1940. In 1941 he stopped smoking and his symptoms were arrested until 1949 when he started to smoke again. Within three months gangrene of three toes developed. Once more after abstinence from smoking and with other therapy the disease became quiescent. In the spring of 1954 he started to smoke cigarettes with a filter tip and this again made the disease active.

Evidence that in this disease the effect of nicotine is peripheral and independent of sympathetic innervation has been obtained by various observers (Silbert, 1935). Smoking aggravates the thrombo-angiitic process in limbs in which the sympathetic fibres have degenerated as a result of sympathectomy. The vasospasm of Raynaud's disease is also brought on in some patients as a result of smoking one or two cigarettes.

The coronary circulation.—Perhaps the most serious suspicion regarding nicotine concerns its effect on the coronary circulation. The direct action of nicotine on the vessels is to dilate them, but it has been shown beyond reasonable doubt that nicotine stimulates the supra-optic nucleus and causes a discharge of vasopressin from the posterior lobe of the pituitary gland. This discharge has been demonstrated by its antidiuretic action (Burn *et al.*, 1945). Now vasopressin causes constriction of the coronary vessels, and the question at issue is whether the amounts of vasopressin discharged during smoking are sufficient to reduce coronary flow. It has been shown that the coronary flow in the dog heart is reduced by about 14% when the amount of vasopressin in the blood is not more than 20 milli-units per litre.

There is no direct evidence yet available. However, Burn and Singh Grewal (1951) have recovered 95 milli-units vasopressin from the urine of one subject who smoked two cigarettes, and they also showed that when vasopressin is injected intravenously, about 5% appears in the urine. From this they calculated that their subject who smoked 2 cigarettes had 1,900 milli-units in his blood, which may be reckoned as 380 milli-units per litre. This concentration would certainly cause a severe reduction in the coronary flow. However, this subject was unusually sensitive to nicotine, and it is unlikely that smoking would normally produce such high concentrations of vasopressin in the blood as this.

The electrocardiogram.—ECG changes have been recorded after smoking. Graybiel *et al.* (1938) found that 20 out of 45 subjects showed a lowering of the T wave, and sometimes an inversion of it. As a result of our studies on atrial fibrillation in Oxford we are coming to the conclusion that this depression of the T wave may indicate a diminution of the active transport of potassium from the plasma into the cardiac muscle, and as the active transport is carried out by metabolic processes which require oxygen, a depression of the T wave may indicate a diminution of the blood flowing through the coronary circulation. Roth *et al.* (1944) also observed a lowering of the T wave. Evans and Stewart (1943) also described a lowering of the T wave.

The ballistocardiogram.—Smoking has been observed to produce changes in the ballistocardiogram (Dock *et al.*, 1951; Caccese and Schrager, 1951; Kelly *et al.*, 1954). The changes were rarely seen in young people, but were common in persons with coronary artery disease. This observation has been confirmed by Starr (1954) who considers that evidence of a change in the ballistocardiogram produced by smoking can be used as evidence of coronary disease.

Conclusion concerning the heart.—Thus the findings all point in the same direction that nicotine has an effect on the heart which, while harmless in the young and healthy person, is harmful in those who are older, and especially in those with coronary disease. This effect may be due to the release of vasopressin which reduces the coronary blood flow, or it may be due to the action of nicotine on chromaffin tissue in the heart causing the release of adrenaline and noradrenaline, which my colleague Kottegoda (1953*b*) has also demonstrated.

I would like to conclude with an expression of surprise that doctors seem often disinclined to tell their patients not to smoke. McDevitt and Wright (1955) speaking of patients with thrombo-angiitis obliterans say "We still encounter a number of patients who have never been told to stop smoking. They frequently submit to multiple sympathectomies, which are quite futile if they continue to smoke". To my mind this is also true in those with

some degree of coronary insufficiency. Such patients ought to be warned quite strictly not to smoke, for when they stop they sometimes improve very much.

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Dr. Richard Doll (Statistical Research Unit, Medical Research Council) *Smoking and Lung Cancer*, said that the data relating smoking to lung cancer were now extensive. Twenty retrospective studies of patients with and without lung cancer in 7 countries had all led to similar conclusions. It seemed unlikely that any form of bias could have accounted for the results of some of the investigations—particularly since it now appeared that the association held only for squamous, oat cell and undifferentiated cancers and not at all for adenocarcinomas. The evidence had been appreciably strengthened by the results of two prospective studies carried out by a different method. In the British inquiry (Doll and Hill, 1956) doctors had been questioned in 1951 about their smoking habits and, in consequence of the replies, had been classified according to the amount they smoked, their method of smoking and whether or not they had stopped smoking. The death-rates subsequently observed in the various groups were very different; the rate for lung cancer was low in non-smokers and increased steadily with the amount smoked till it was more than twenty times higher among heavy smokers. A similar, but much less pronounced, trend was observed for chronic bronchitis and a slight trend was observed for coronary thrombosis. For other cancers and for all other diseases taken together there was no significant difference in mortality between the various smoking categories. Cigarette smokers showed a higher mortality from lung cancer than pipe smokers and there had been a higher mortality among those who were still smoking in 1951 than among those who had stopped. The lung cancer mortality among doctors who were continuing to smoke 25 or more cigarettes a day at the time of completing the questionnaire was forty times that among non-smokers. The latest results in the American Cancer Society's study had been reported by Dr. Hammond to a meeting of the American Statistical Society in December 1955. This study involved the follow-up of 200,000 men aged 50–69, who had been interviewed by volunteer members of the Society in 1952. The results with regard to lung cancer were closely similar to those of the British study; the mortality had been some ten times higher among cigarette smokers than among non-smokers, higher still among heavy smokers and higher among cigarette smokers than among pipe or cigar smokers.

It was difficult to attribute the results of these two investigations to a tendency for doctors to diagnose lung cancer more readily among heavy cigarette smokers, since the association with smoking was stronger for histologically proven cases than for all cases. Neither could it be due to the effect, postulated by Berkson (1955), of special selection of persons to be included in the study as a result of reticence on the part of heavy smokers to respond to questions about their smoking habits. Such an effect should wear off in the course of a few years, but in the British study the relationship with smoking had remained unaltered over four years, while in the American study it was becoming stronger with the passage of time. It could not be that smoking merely determined the site in which a predetermined cancer developed, since in this case there would need to be a lower mortality from forms of cancer other than lung cancer among heavy smokers—and this was not observed. The simplest explanation of the facts was that cigarette smoking was a major cause of lung cancer. It was impossible to exclude the possibility that the association might be indirect, but in so far as any such mechanism had been suggested which was capable of testing, this had been disproved. For example, the association did not arise because heavy smokers specifically tended to live in big towns where they were exposed to atmospheric pollution. In the British investigation the smoking habits of the doctors were much the same wherever they lived, whereas in the American investigation, which was on a larger scale, it had been possible to show that the relation with smoking held—and was in fact much the same—in all types of residential area. The suggestion that the fundamental factor might be alcohol consumption was disproved by the work of Wynder *et al.* (1956) who showed that there was no significant difference between the amounts of alcohol drunk by patients with and without lung cancer, if the amounts smoked were kept constant.

The conclusion that cigarette smoking was a major cause of lung cancer accorded well with many of the other observed facts about lung cancer. For example, a detailed pathological study of the bronchial mucosa of patients dying of various types of cancer had shown that hyperplasia and metaplasia of the basal cell layer and the presence of carcinoma-in-situ became progressively more common as the amount smoked increased and was commonest of all among patients who had died of lung cancer. The increase in the death-rate in this country had followed the increase in cigarette consumption by about twenty years; it had been more rapid than the increase in cigarette consumption but some of the increase in the death-rate must be attributed to improvements in diagnosis. It remained to be seen whether the lung cancer death-rate would become stable in the future, following the relative stabilization of cigarette consumption over the last decade. The difference in the recorded mortality in different countries correlated well with the annual consumption of cigarettes in those countries twenty years previously; the mortality in Britain was, however, somewhat higher and the mortality in the U.S.A. somewhat lower than would be expected from comparison with other countries. The ratio of the recorded death-rates among men and women accorded with what was known of the past smoking habits of the two sexes.

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Dr. Neville Oswald (Physician St. Bartholomew's Hospital and Brompton Hospital): *Medical Effects of Smoking*

Clinical aspects.—Of the dozen or so alkaloids which have been isolated from the tobacco plant, nicotine has established itself as being the most important. The pharmacological properties of nicotine are now well understood, the main effect being upon the sympathetic nerves, which are first stimulated and later, if the dosage be sufficient, paralysed. It is a stimulant to the central nervous system, and in toxic doses may produce convulsions. As with other habit-forming drugs, experimental investigations have been hampered, both in man and animals, by the differences in response to large and small doses in those who have or have not been previously exposed.

The vaso-constrictor effect is seen clinically in peripheral vascular disease and angina pectoris. Whilst no one would claim that either of these diseases was caused by smoking, the symptoms are occasionally intensified by it, and at least a trial period of abstinence should be recommended. Thrombo-angiitis obliterans, if indeed such an entity exists, falls into a rather different category, as it seems to bear a direct relation to smoking, so that smoking should always be forbidden in this disease.

The only parts of the gastro-intestinal tract that are affected by tobacco, so far as is known, are the stomach and duodenum, in which the symptoms of functional dyspepsia and peptic ulceration are thought to be aggravated. This is borne out in clinical practice, and the abandonment of smoking, especially when active ulceration exists, must be regarded as an essential part of proper medical management. It may be as well to remember that, in health, roughly 100 ml. of bronchial secretions are transferred from the trachea to the stomach via the œsophagus in each twenty-four hours and if these, together with saliva, are charged with the products of combustion of tobacco, they are likely to contribute to any effects that blood-borne nicotine may have upon the nerve endings in the gastro-duodenal mucosa. Certainly there seems to be a close association between smoking and minor symptoms of dyspepsia, particularly heartburn.

Amongst other clinical effects of smoking, the transient rise in blood pressure and pulse-rate, extrasystoles and the anti-diuretic effect are not important so far as we know, but smoking in conjunction with malnutrition seems to predispose to amblyopia.

A recital of the possible ill-effects of nicotine may leave the impression that the drug is capable of causing or aggravating a wide variety of diseases. This is offset to a large extent by the pleasant effects, which are related to the central nervous system; were this not so, there would be no problem. Most fresh smokers need to pass through a short period of initiation, which indeed is an accepted part of undergraduate experience. The phases of dizziness, nausea and vomiting are well known, but acute toxic manifestations, such as stupor and convulsions, are very rare. Repeated smoking leads to addiction, in which nicotine is said to soothe the nerves, relieve tension and monotony, and enable a clear brain to be maintained. Certainly, these are the properties which habitual smokers claim to exist.

In recent years, an association between tobacco smoking and bronchial carcinoma has been alleged by medical statisticians. Their case may now be regarded as proved, but clinicians have been slow to act upon this information, principally because of the reluctance of the majority of them to abandon the habit themselves. At first, the evidence was based upon small numbers of deaths from bronchial carcinoma, but reports from various countries during the past year or so confirm the association, which can be no longer disputed. Whether statistical methods will ever be able to determine the extent of the association remains to be seen. Some authors have gone so far as to suggest that heavy smokers have one chance in twenty of dying from bronchial carcinoma, and are twenty times more likely to do so than non-smokers. Perhaps such generalizations should be avoided until more is known of the other variable factors which influence the development of this neoplasm.

By dividing the population into heavy, medium, light and non-smokers, available evidence points to an association between the amount smoked and the chances of developing a bronchial carcinoma. In other words, there is a critical end-point of irritation beyond which epithelial metaplasia takes place. Perhaps future research will be able to determine the extent to which smoking influences this end-point in relation to such other possible predisposing causes as air pollution and a familial tendency to cancer. Clearly, the application of statistical methods can do no more than define the problem, and the real necessity now is for more intensive work upon the isolation of carcinogens from burnt tobacco, such as 3-4 benzpyrine, in the hope that possible noxious substances may be eliminated from tobacco without destroying its pleasant qualities.

The study of smoking in relation to chronic bronchitis is considerably hampered by our lack of a satisfactory definition of chronic bronchitis. The first difficulty is that about one-half of the population have mild respiratory symptoms from time to time which are not sufficiently severe to be labelled bronchitis, but which include the so-called "smoker's cough". Beyond this, with no sharp dividing line, are the true bronchitics who are disabled by one or more of the triad of infection, diminished air-flow, and reduced alveolar surface. In order to determine whether the possible effects of smoking could be expressed in figures, a form was completed upon 5,844 clerical workers in two London offices of the Civil Service. In this way, comparable groups of males and females were obtained having similar age, work, incomes, domestic circumstances and exposures to respiratory infections. The results (Table I) show consistently higher figures both for bronchitis and mild respiratory symptoms in smokers, compared with non-smokers, and are of the order which might be anticipated from clinical impressions. No estimate can be made of the quantitative effect of tobacco upon respiratory symptoms from this series, because some of the figures are insufficiently large for the differences to be statistically significant, but the consistent trends towards a higher prevalence of symptoms among smokers is most unlikely to be fortuitous. Table I also shows the higher prevalence of bronchitis in the older age

TABLE I.—PREVALENCE OF MILD RESPIRATORY SYMPTOMS AND BRONCHITIS IN 5,844 CLERICAL WORKERS (3,602 MALES, 2,242 FEMALES) IN THE CIVIL SERVICE IN LONDON, ACCORDING TO SMOKING HABITS (Oswald and Medvei, 1955)

	Age 15–39		Age 40–65	
	Smokers	Non-smokers	Smokers	Non-smokers
Males:				
No respiratory symptoms..	276 (40·6%)	255 (49·9%)	674 (34·8%)	260 (54·9%)
Mild symptoms	340 (50·0%)	235 (46·0%)	906 (46·8%)	139 (29·3%)
Bronchitis	64 (9·4%)	21 (4·1%)	357 (18·4%)	75 (15·8%)
Total	680	511	1,937	474
Females:				
No respiratory symptoms..	159 (40·6%)	352 (54·1%)	198 (34·3%)	317 (51·0%)
Mild symptoms	193 (49·2%)	258 (39·6%)	271 (46·9%)	229 (36·9%)
Bronchitis	40 (10·2%)	41 (6·3%)	109 (18·8%)	75 (12·1%)
Total	392	651	578	621

group in both sexes. This is hardly surprising, but the close correlation between the prevalence of bronchitis and sex in each group of smokers and non-smokers is remarkable, strongly suggesting that, when age, domestic and working conditions are standardized, the different rates for bronchitis in men and women are related to smoking habits.

The tobacco habits of 1,000 bronchitics have been investigated at the Bronchitis Clinic, Brompton Hospital. All except 106 had smoked at some time, and they were asked their opinions of the effect of smoking upon their bronchitis. The results are set out in Table II.

TABLE II.—TOBACCO HABITS OF 1,000 BRONCHITICS (Oswald *et al.*, 1953)

	Yes	No	Don't know
Does smoking aggravate bronchitis?	479	381	34
Has smoking been abandoned or cut down because of bronchitis?	532	359	3
If "yes", has bronchitis improved?	395	136	1

The majority agreed that their bronchitis was aggravated by smoking and a surprisingly high proportion of them had cut down or abandoned the habit with benefit.

The precise relationship between smoking and bronchitis cannot be defined. The suggestion has been made that tobacco smoke acts as a chemical poison upon the bronchial epithelium; certainly, it promotes the excessive formation of mucus, and it seems to predispose to chronic bronchitis. Its effects are likely to be influenced to some extent by individual differences in response to bronchial irritation. The commonest effect is the expectoration of mucoid sputum, which diminishes rapidly on the cessation of smoking, at least in the early stages; later, the condition may become permanent, causing little disability. At any stage in this process, bronchospasm may supervene, in which case breathlessness becomes apparent, and the sooner smoking is abandoned the better; unfortunately, once clinical bronchospasm has become evident, it is extremely difficult to eradicate unless it does so fairly promptly on the withdrawal of tobacco.

The excessive formation of bronchial mucus from any cause, and one cause is undoubtedly tobacco smoking, inevitably leads to a predisposition towards bronchial infection the so-called "resistance lowering effect" of mucus. To this extent, smoking hastens the onset of true chronic bronchitis, in which clinical evidence of an infective element exists, and this effect may well be enhanced by any poisonous action that tobacco smoke may have upon the bronchial epithelium.

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Clinical Section

President—Sir HENEAGE OGILVIE, K.B.E., D.M., M.Ch., F.R.C.S.

[*March* 8, 1957]

MEETING HELD AT THE WHITTINGTON HOSPITAL, LONDON

Intrahepatic Portal Hypertension Due to Mucoviscidosis.—T. ST.M. NORRIS, M.D., M.R.C.P., D.P.H.

The association between cirrhosis of the liver and fibrocystic disease of the pancreas was first noted by Anderson in 1938, and in 1944 Farber when reviewing the post-mortem findings in 87 cases of the latter condition mentioned that in a small number he had found an unusual type of cirrhosis which appeared to be secondary to intrahepatic biliary obstruction. He held that the sequences leading to these obstructive changes were similar to those seen in the pancreas.

During the last ten years it has been recognized that hepatic cirrhosis may be one of the features of fibrocystic disease of the pancreas and its incidence according to different authorities is shown in Table I.

TABLE I.—INCIDENCE OF HEPATIC FIBROSIS AS A FEATURE OF FIBROCYSTIC DISEASE OF THE PANCREAS

Authority	Year	No. of cases reviewed	No. of cirrhotics	Percentage cirrhotics
Bodian	1952	62	"About a quarter"	25%
Webster and Williams ..	1953	116	5	4·4%
May	1954	"Several Hundred"	1	Less than 1%
Craig *et al.*	1955	160	7	4·37%
Sant' Agnese and Blanc..	1956	116	25	22%

Sant' Agnese and Blanc (1956) state that one-third of the cases of cirrhosis seen in children of the pædiatric age-group is due to fibrocystic disease of the pancreas.

CASE REPORT

A schoolgirl aged 14 was admitted to the Archway Wing of the Whittington Hospital on October 26, 1956, because of hæmatemesis. There was nothing unusual in the family history, the father and mother, who are not cousins, are alive and well, one brother aged 9 is apparently well.

There were no previous illnesses until the age of 4 when the child had whooping cough; since that illness she has suffered from recurrent "colds" and cough. At the age of 11 because of a cough, she was X-rayed and hepatomegaly without splenomegaly was noted, chest X-ray was normal. Her serum albumin was 5·1 g.% and serum globulin 3·5 g.%.

Diagnosis: cirrhosis of the liver.

On admission to the Whittington Hospital she gave a history of hæmatemesis on the previous day with recurrence on two occasions since; there had been no dyspepsia, but diarrhœa with the passage of pale bulky stools had been noted.

On examination she was pale with a hæmoglobin of 48%. The liver edge was palpable two to three fingerbreadths below the costal margin and the spleen, though not felt on admission, was palpable two days later. Naked-eye examination of the stools showed them to be pale and unusually bulky.

She made a satisfactory recovery from the hæmorrhage and the following investigations were carried out.

Chest X-ray.—A small area of diminished translucency is seen in the right infra-clavicular region (Fig. 1); this is probably healed pulmonary tuberculosis. The diaphragm is not flattened and the intercostal spaces not broadened.

Barium swallow.—Filling defects in the lower third of the œsophagus are characteristic of varices (Fig. 2).

Barium meal.—Small duodenal ulcer.

Follow through.—N.A.D.

X-ray lumbar spine and right femur.—Nothing abnormal.

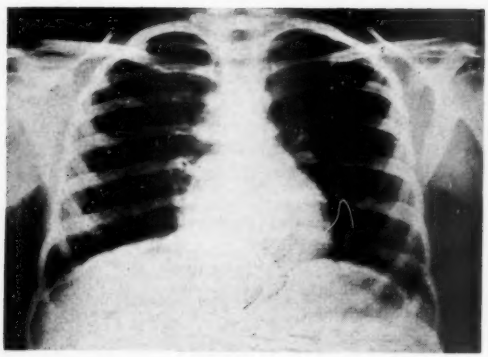


FIG. 1.



A B C

FIG. 2.

Hb 48%. W.B.C. 6,700 (polys. 61%, eosinos. 1%, lymphos. 34%, monos. 4%).

Prothrombin time: 21 seconds. Control 15 seconds. Serum proteins 6·2, albumin 3·8, globulin 2·4 grams.%. Paper electrophoresis of serum proteins: N.A.D. Serum bilirubin 0·1 mg./100 ml. Alkaline phosphatase 21·5 units/100 ml. Thymol turbidity 3 units/100 ml. Bromsulphthalein test normal. Absolute indices on day after admission: Hb 43%. P.C.V. 20%. M.C.V. 91 cμ. M.C.H.C. 32%.

C.S.U.: N.A.D. W.R. and Kahn negative. Serum calcium 10·4 mg.%. Serum inorganic phosphorus 5·6 mg.%.

Duodenal intubation was attempted but was not satisfactorily completed because the patient became distressed. However, it was established that trypsin, bilirubin and bile salts were present in the duodenal juice. Tryptic activity was present in dilutions up to 1 in 50 and in fæcal dilutions up to 1 in 100. (Normal dilutions of 1 in 50 to 1 in 100.) Fat balance showed average daily excretion of 22·7% of intake. Glucose tolerance curve showed an increase of 92 mg.% above resting value 60 minutes after glucose feed. No glycosuria. Urinary calcium: 0·15 gram in a total of 1,450 ml. Folic acid absorption test normal. Sweat test: Sodium 122 (normal 4–52), chlorides 129 (normal 9–40) m.eq./litre.

In January 1957, at laparotomy by Mr. W. W. Davey, no duodenal ulcer was found, but the liver was coarsely nodular and unusually firm. A small portion was taken for section which showed a coarse fibrosis in the portal systems with areas of acute and chronic



FIG. 3.—Very low power showing groups of normal lobules with coarse and irregular portal fibrosis. × 8.

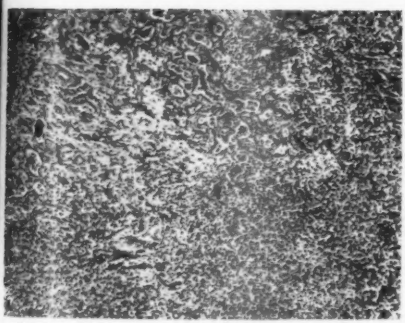


FIG. 4.—Low power showing an area of portal fibrosis with chronic inflammation and a few concretions in bile ducts. × 53.

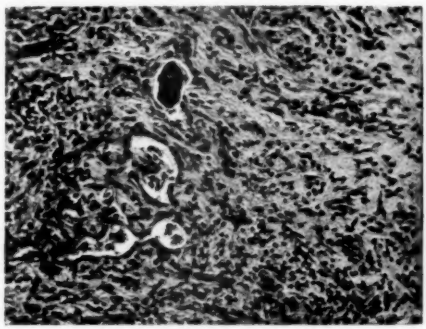


FIG. 5.—High power of Fig. 4 to show concretions. × 133.

inflammatory infiltration and conspicuous proliferation of bile canaliculi containing eosinophilic secretion and some concretions (Figs. 3, 4, 5).

There is no doubt that this girl suffers from an unusual type of hepatic cirrhosis which is associated with steatorrhœa. The diagnosis seems to lie between cirrhosis due to fibrocystic disease of the pancreas or mucoviscidosis and a nutritional cirrhosis secondary to dysfunction of the small intestine and malabsorption.

In favour of the former diagnosis we have: The sweat test. The liver biopsy. The normal folic acid excretion test and absence of evidence of any intestinal abnormality. The evidence in favour of the latter diagnosis is negative only, being:

The tryptic activity in the duodenal aspirate and the absence of radiological evidence of emphysema or bronchiectasis.

We are satisfied that the former is the correct diagnosis.

If we accept this diagnosis we are faced with a problem regarding treatment. Should this girl be submitted to surgery with a view to a shunt operation? or should she be treated conservatively? In considering this problem a summary of Sant' Agnese and Blanc's 5 cases in which the diagnosis was confirmed by liver biopsy may be helpful (Table II).

Case 1 died of pulmonary complications.

Case 4 died after three operations, the first a lieno-renal shunt; this thrombosed and hæmatemesis recurred. A porta-caval shunt was then carried out, but again hæmatemesis

TABLE II.—SUMMARY OF SANT' AGNESE AND BLANC'S 5 CASES

Sex	Age	Duodenal tryptic activity	Sweat Cl.	Sweat Na.	Lung involvement	Gastro-intestinal bleeding	Shunt operation	Present state
M	4	0	78	—	+	+	+	Died 18/12
M	6	0	94	95	+	+	+	Well 2/12
M	6	320 units per ml.	98	120	+	0	0	Alive
F	10	0	72	84	+	+	+	Died 19/12
F	10	131 units per ml.	84	95	+	+	+	Alive 6 years
			CASE UNDER REVIEW FOR COMPARISON					
F	14	1–100 dilution Normal 1–50 to 1–600	129	122	History only	+	0	

recurred. A third operation was attempted, but the girl did not long survive and at post-mortem it was found that the portal vein had thrombosed.

In the case under review it is a difficult decision to make. Firstly there is the slight possibility that the hæmorrhage originated in the duodenal ulcer and not from œsophageal varices. Secondly, this disease involves other important organs such as the lungs and the pancreas besides the liver, and the expectation of life is in any event not beyond the middle twenties.

It therefore seems rather drastic to resort to major surgery at present and my own view is that she should be kept under close observation on conservative treatment.

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Myeloproliferative Syndrome presenting as "Neutrophilic Leukæmia".—A. N. EXTON-SMITH, M.D., M.R.C.P. (with the assistance of A. A. CHAZAN, M.B.).

L. P., female, aged 80.

History.—Swelling of the legs and general weakness for three months. Constipation and prolapse of the bowel for about six months.

On examination (22.9.56).—Anæmic; signs of congestive cardiac failure; well-marked rectal prolapse which could easily be reduced.

Progress (24.9.56).—Hæmoglobin 44% (*see* Table I). The anæmia was treated with

TABLE I.—SUMMARY OF BLOOD FINDINGS

Date	Hb%	W.B.C.	Neutros. %	Eosinos. %	Basos. %	Lymphos. %	Monos. %	Comments on film	Platelets	E.S.R.
24.9.56	44	63,600	97	—	—	1	2	Iron-deficient R.B.C.s with increased polychromasia and a few normoblasts. Adult W.B.C.s and the polymorphs showed a shift to the right		21 mm.
18.10.56	55	37,200	96	1	—	3	—	No primitive cells seen	1,185,000	14 mm.
13.11.56	73	62,000	90	3	2	5	—	Platelets numerous. One myeloctye noted		
28.12.56	105	71,200	93	1	—	5	1	No primitive cells seen		2 mm.
25.1.57	102	61,800	93	2	—	4	1	No primitive cells seen	786,000	2 mm.

Imferon. Enlargement of the spleen was detected for the first time on 19.10.56. General condition gradually improved and the signs of cardiac failure disappeared during the next two months. Present condition: fully ambulant, colour good, spleen 3 cm. below costal margin.

Investigations.—Table I gives a summary of the blood findings. 23.11.56 and 30.1.57: *Sternal Puncture*—Marked hyperplasia of erythroid, myeloid and megakaryocytic elements (*see* Figs. 1 and 2). Fæcal occult blood reaction negative. Barium enema unsuccessful.

13.2.57: *Blood* (*see* Fig. 3). R.B.C. 6,880,000; Hb 117%; P.C.V. 58%. M.C.V. 85 cμ. M.C.H.C. 29·9%. W.B.C. 65,800 (neutros. 93%, eosinos. 4%, basos. 1%, lymphos. 1%, monos. 1%). *Platelets* 922,000 per c.mm. *Film:* Low-grade increase in polychromasia but no primitive red or white cells seen.

22.1.57: Serum vitamin B_{12} 1,000 μμ/ml.

14.2.57: Leukocyte alkaline phosphatase (*see* Fig. 4)—marked increase.

Comment.—The early hæmatological features suggested the diagnosis of neutrophilic leukæmia, and the findings in the peripheral blood are similar to those described by Tuohy (1920). Subsequently, however, polycythæmia developed and the later blood examinations disclosed a pancytosis. These changing hæmatological features support the unitarian hypothesis of the myeloproliferative syndromes (Dameshek, 1951). The occurrence of neutrophilia in polycythæmia vera is well recognized (Weber, 1933; Rosenthal and Bassen, 1938), but for polycythæmia to present with such a marked neutrophilia without immature white cells in the peripheral blood is most unusual. Estimation of the leukocyte alkaline phosphatase activity by the histo-chemical method of Wiltshaw and Moloney (1955) shows a marked increase with intense staining in the cytoplasm of most leucocytes (*see* Fig. 4); this reaction is found in the leucocyte abnormality of polycythæmia vera and is unlike the results obtained in chronic myeloid leukæmia.

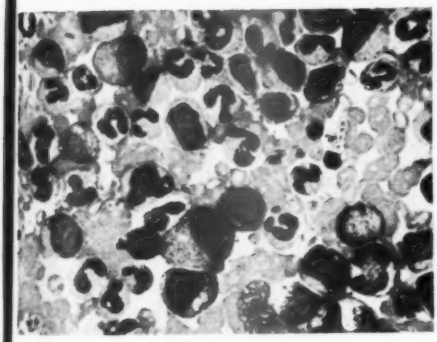


FIG. 1.

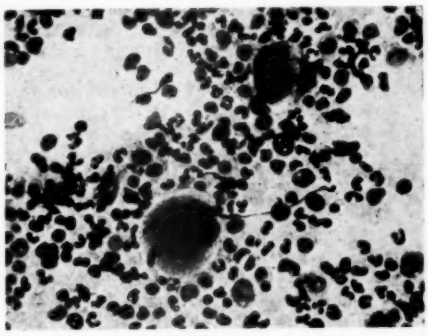


FIG. 2.

FIGS. 1 and 2.—Bone-marrow; myeloid and megakarocytic hyperplasia. (Fig. 1 ×426; Fig. 2 ×222).

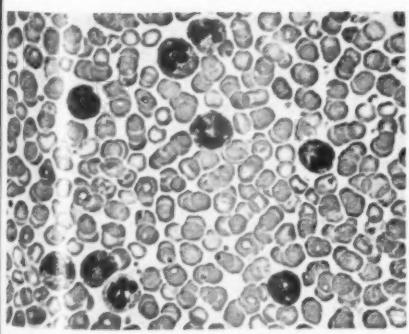


FIG. 3.—Peripheral blood (13.2.57); marked neutrophilia. ×426.

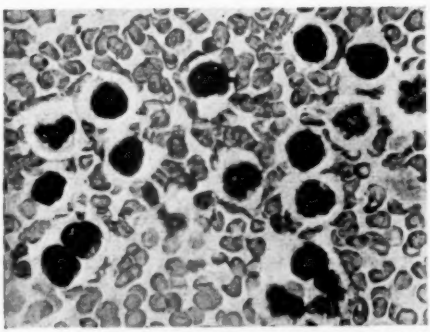


FIG. 4.—Leucocyte alkaline phosphatase; marked staining of cytoplasm of leucocytes. ×426.

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Bilateral Uretero-Sigmoidostomy, Acidosis, Osteomalacia.—ARNOLD BLOOM, M.D., M.R.C.P.

R. R., male, aged 45. September 1953: Total cystectomy and transplantation of ureters into colon performed for carcinoma of bladder (Mr. P. T. Savage). Defaulted on after-care and readmitted in January 1954 with thirst, an "ammonia taste" in the mouth, lassitude, anorexia and vomiting. Blood chemistry revealed acidosis and hypokalæmia (alkali reserve 12·1, serum potassium 3, sodium 126, chlorides 90 mEq./l. blood urea 120 mg./100 ml.). Potassium bicarbonate by mouth led to rapid improvement and correction of biochemistry (alkali reserve 22·2, potassium 6·7, sodium 141, chlorides 101mEq./litre: urea 50 mg./100 ml). He was again admitted in April 1954 with a similar relapse and response to therapy. Thereafter, he took alkalis sporadically but failed to attend out-patients: for the six months prior to his last admission, he developed increasing weakness in the limbs and became almost unable to get out of bed. When seen in November 1956, some three years after cystectomy, he walked slowly and stiffly, with a waddling gait and using two sticks. To get out of a chair, he "climbed up himself", i.e. hands on knees, then up his thighs. There was marked tenderness over the entire thorax, especially over left second rib. Transverse abdominal creases and loss of head to pubic height suggested collapsed vertebræ (crown to pubis 32 in., pubis to feet 34 in., span 71 in.). Muscles were weak and spastic with myotonic irritability and increased reflexes. Plantars flexor.

Investigations.—X-rays: rarefaction of vertebral column with marked wedging of thoracic vertebræ (Fig. 1): fracture of left second rib. Intravenous pyelograph: kidneys failed to visualize.

Bone biopsy (Von Kossa stain of undecalcified cancellous bone): numerous pale osteoid borders on surfaces of dark calcified portions of bone trabeculæ: excessive fragmentation of bone trabeculæ is an artefact: appearances typical of osteomalacia (Fig. 2).

Biochemistry: Calcium 8·2, phosphorus 3·5 mg./100 ml.
Alkali reserve 12·1, chlorides 111, sodium 130, potassium 3·6 mEq./l.
Alk, phosphatase 14·5 KA units. Acid phosphatase 1·5 units.
Protein: albumin 3·2, globulin 2·8 grams%.
Blood urea 60 mg./100 ml.



FIG. 1.—Partial collapse of vertebral bodies.

Treatment and progress.—On the suggestion of Professor C. E. Dent, calciferol alone (15 mg. I.V. followed by 5 mg. I.V. twice weekly) was administered for two weeks, but with no improvement. Calciferol by mouth (3·5 mg. daily) and alkalis (sodium lactate 2 grams and potassium bicarbonate 1 gram t.d.s.; later sodium bicarbonate 3 grams t.d.s.) were then administered. He was given a low salt diet and advised to empty his bowels at frequent intervals. Over the next three months, progress was steady; he became able to walk freely without sticks, and could get up from a chair without use of his hands. No chest tenderness. February 1957: X-ray of chest showed callus formation at site of rib fracture. Bone biopsy: "The osteoid borders have disappeared. One or two localized areas of narrow fibrosis and irregularity of cement lines suggest remodelling following mild trauma."

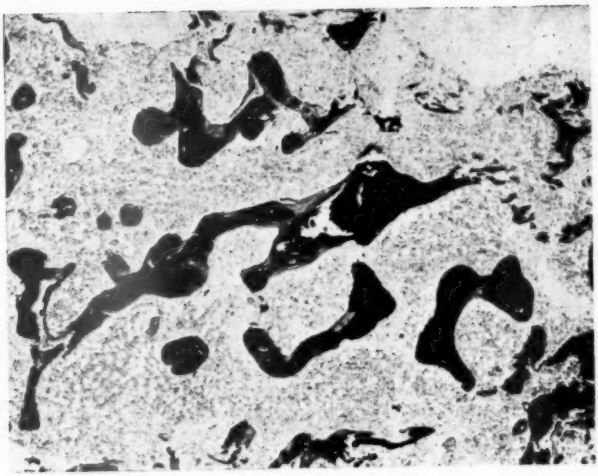


FIG. 2.

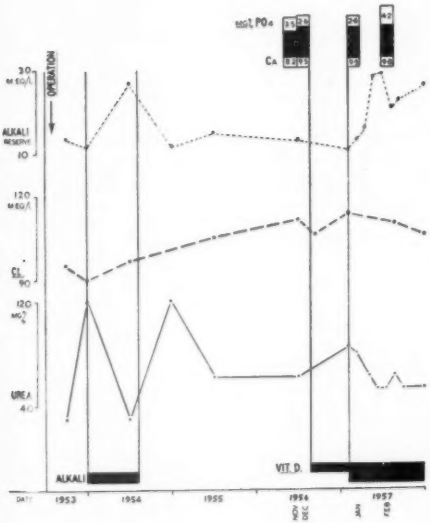


FIG. 3.

FIG. 2.—Bone biopsy showing osteoid borders. ×17.

FIG. 3.—Chart showing effect of alkali on biochemistry.

Calcium 9·8; phosphorus 4·2 mg./100 ml; alkali reserve 22·2, chlorides 107 mEq./l. (Fig. 3.)

Comment.—Two mechanisms may be responsible for the persistent acidosis occurring after uretero-sigmoidostomy. Firstly, there appears to be a selective absorption from the lower bowel of urinary chlorides, perhaps combined with ammonia derived from bacterial breakdown of urea. Secondly, since the kidneys are usually damaged by chronic retrograde infection, the renal acid-base regulating mechanism is disturbed and the acidosis cannot be corrected. Prolonged acidosis in its turn leads to loss of fixed base. In this patient, although initially there was hypokalæmia, in the later stages the most striking feature was resorption of calcium from the bones and consequent osteomalacia. These symptoms can be avoided by daily administration of alkalis, by restriction of salt and by frequent emptying of the lower bowel. However, the likelihood of electrolyte imbalance

is a serious disadvantage of bilateral uretero-colostomy, particularly in this case where the patient was unco-operative.

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Mr. E. W. Riches hoped that the occasional occurrence of severe acidosis would not lead to the complete abandonment of the operation of uretero-sigmoidostomy. When the kidneys were not grossly damaged before operation there was no reason to condemn the patient to a permanent urinary fistula, and acidosis could be avoided by giving alkalis, reducing salt intake, and insisting on regular three-hourly evacuation of the rectum. How many would prefer an ileostomy with the need to wear an appliance rather than a controlled rectal bladder? If the kidneys were damaged uretero-ileostomy made it possible to save them from further injury, and had a useful place in the treatment of carcinoma of the bladder.

He had seen one case of osteomalacia following uretero-sigmoidostomy. This patient also had defaulted in taking alkalis, and had eventually gone to another hospital where the condition had not been recognized; orthopædic rather than biochemical methods of treatment had been instituted without success. Under treatment by alkalis he had made a good recovery.

Cervical Pain as a Symptom of Hypotension During Treatment with Ganglio-plegic Drugs.—E. MONTUSCHI, M.D., M.R.C.P.

G. T., male, aged 45.

History.—First seen in 1953 with a spontaneous left pneumothorax which resolved with bed rest. B.P. 180/100.

In 1954 he was admitted for congestive cardiac failure. Auricular fibrillation. B.P. 240/160. Cardiac enlargement. Left ventricular hypertrophy on clinical examination and in ECG. Good renal function.

Treatment started with digitalis and pentolinium; the dose of Ansolysen Retard was gradually increased to 25 mg. in the morning. The congestive failure cleared and he was followed up in out-patients. He then reported that at the height of the effect of the drug, one to one and a half hours after injection, he would experience severe pain in the posterior cervical region on standing and on physical exertion; the pain would subside on lying down. The symptom would disappear in the afternoon, whatever the posture.

Readmitted to hospital in September 1956 when a change was made from pentolinium by injection to Mecamylamine by mouth. On that occasion serial blood pressure readings were taken after an injection of pentolinium.

Since taking Mecamylamine there has been no recurrence of posterior cervical pain.

On examination.—Fundi show hypertensive retinopathy with hæmorrhages. Pulse 80. Auricular fibrillation. Considerable cardiac enlargement with heaving apex beat. Wide splitting of first and second sounds at all areas. The split of the second sound widens on inspiration. No evidence of congestive cardiac failure. ECG tracings show a change from left ventricular hypertrophy pattern to right bundle branch block.

Comment.—This patient was the first of a series of six to draw my attention to a symptom not described before.

The symptom is pain in the nape of the neck which is severe, radiating across the shoulders when a rapid fall in blood pressure caused by ganglio-plegic drugs reaches its lowest point. The pain is aggravated by exertion and immediately corrected by assuming a reclining posture. No ECG changes, suggestive of myocardial ischæmia, have been recorded at the height of the symptom. If patients are unaware of its cause pain may be prolonged and lead to misdiagnosis. One patient had been referred to the physiotherapy department for cervical spondylosis. No explanation is offered as to the mechanism of this symptom.

Idiopathic Hypercatabolic Hypoproteinæmia.—W. R. CATTELL, M.B., M.R.C.P. (for T. St. M. NORRIS, M.D., M.R.C.P., D.C.H.).

Mr. A. W., a librarian's assistant, aged 20, was admitted to the Archway Wing of the Whittington Hospital in March 1956, with a history of ankle swelling for ten days. In addition, he had had malaise and lassitude for some months and a history of mild constipation with abdominal discomfort for many years. His diet was normal in quality and quantity.

There was no history of serious illness in the past. He had had the usual childhood exanthemata without complications. At the age of 17 years he developed mild flexural eczema which has persisted. There was no history of acute allergic disorders.

There was no relevant family history. He is an only child.

On examination he was pale and thin, but appeared normally developed. There was slight œdema of both ankles but no evidence of cardiovascular disease. He also had a dry flexural eczema affecting the elbow and popliteal areas. There was slight abdominal distension but no abnormal masses and no hepatic or splenic enlargement. All other systems were normal.

Estimation of his serum proteins showed a hypoproteinæmia, the total serum protein on admission being 4 grams/100 ml. Subsequent examination showed that the hypoproteinæmia affected albumin and globulin alike and paper electrophoresis showed reduced albumin, much reduced gamma globulin and increased alpha globulin.

Other special investigations were as follows:

Hb 58% (8·5 gram/100 ml.). R.B.C. 4,370,000. P.C.V. 32%, M.C.V. 73 cμ., M.C.H.C. 27%. W.B.C. 6,450 with normal differential count and no eosinophilia. Fæcal trypsin was present in normal quantities; F.T.M. normal; fat balance—average daily excretion of 3·8% of fat intake; fæcal nitrogen excretion 0·5 gram daily while on intake of 70 grams daily. Sigmoidoscopy normal; Ba meal and follow through normal; straight X-ray of abdomen normal; Ba enema showed dilatation of the whole length of the colon and rectum—the appearances being consistent with those found in chronic constipation. Serum bilirubin 0·2 mg./100 ml., alkaline phosphatase 3 units (King Armstrong), thymol turbidity 2 units/100 ml., bromsulphthalein excretion normal; prothrombin time 18 seconds against control of 15 seconds. Liver biopsy (3.5.56) showed slight œdema of otherwise normal liver tissue. Repeated urinalysis showed no proteinuria and no abnormality on microscopic examination of the centrifuged deposit. Blood urea <20 mg./100 ml. Water concentration and dilution test was normal. Examination of the urine by two dimension paper chromatography showed no abnormal amino-aciduria. Serum calcium 8·7, inorganic phosphate 2·7, cholesterol 143 mg./100 ml. Wassermann and Kahn reactions negative. Mantoux positive to 100 T.U. only. X-ray of chest normal.

His mother (his only close living relative) had her plasma proteins estimated and these were normal, as was the electrophoretic pattern.

A diagnosis of idiopathic hypoproteinæmia was made and the patient was given a high protein diet (average daily intake of protein being 100–120 grams). He was also given oral iron and the iron deficiency anæmia rapidly improved, although the Hb has never reached 100%. A mild iron deficiency anæmia persists (Hb 84%, R.B.C. 5,200,000, M.C.V. 78 cμ., and M.C.H.C. 30%). and is associated with weakly positive stool benzidine tests. The exact site of this intestinal bleeding has not been located.

His œdema rapidly disappeared after admission to hospital and has only occasionally been noted since. As can be seen from Table I there has been no significant change in his serum protein levels over twelve months, despite a high protein intake.

TABLE I.—SERUM PROTEINS

	Total serum proteins grams/100 ml.	Albumin grams/100 ml.	Globulin grams/100 ml.	A/G Ratio
Normal	6·3–8·2	3·5–5·7	1·5–3·0	
24.3.56	4			
9.4.56	4·2			
27.4.56	4·3			
11.5.56	4 2	2·8	1·4	2/1
2.7.56	4·2	2·6	1·6	1·6/1
20.8.56	3·9	2·8	1·1	2·5/1
18.12.56	4·2			
2.3.57	4	2·9	1·1	2·8/1

In February 1957 studies were carried out to determine the fate of intravenously injected human serum albumin labelled with radioactive iodine. Figs. 1 and 2 show the fate of intravenously injected labelled serum albumin in a normal young man and in this case. It will be seen that the initial fall off in plasma levels is similar in each case and represents mixing of the labelled albumin with native albumin throughout the body. The subsequent fall in plasma levels can be taken to represent the gradual elimination or breakdown of the injected albumin. If the daily urinary output of radioactive iodine is measured over this period it can be shown that paralleling the fall off in plasma radiaoctivity, there is actual elimination of radioactive iodine in the urine and if the twenty-four-hour urine radioactivity is divided by the total radioactivity in the plasma at the middle of the twenty-four-hour period, one may estimate the proportion of plasma albumin broken down per

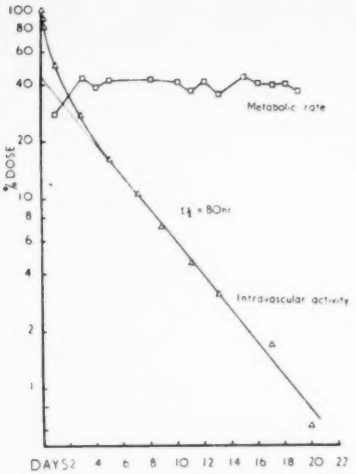


FIG. 1.—Idiopathic hypoproteinæmia.

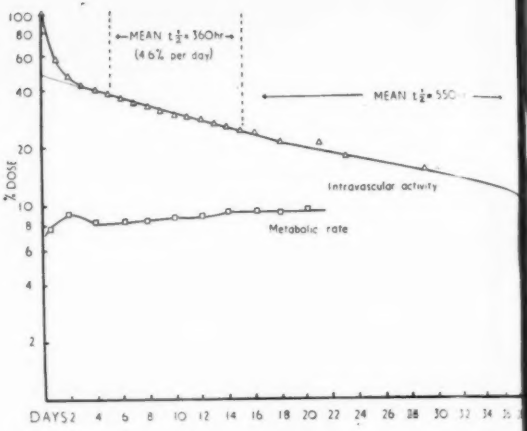


FIG. 2.—I^{131}—Human albumin in normal human.

day. This is represented in the graph as the "metabolic rate"—expressed as a percentage of total plasma albumin.

It can be seen that there is a marked difference in the metabolic rates in the normal and in this case. It would, therefore, seem that in the patient there is an excessively rapid breakdown of plasma albumin (and probably other plasma proteins) within the body. As his plasma protein levels remain relatively constant, we must presume that to meet this excessive breakdown, the rate of synthesis must be increased.

The findings in this study agree with those of Schwartz and Thomsen (1957) using similar methods. Both studies combine to oppose the originally held view that the underlying defect in this condition is one of defective synthesis of plasma proteins. They do not, however, indicate the site of this abnormal breakdown or the primary cause of such a disturbance in plasma protein metabolism. We propose to carry out further studies in this case in an attempt to elucidate these points further.

We would like to acknowledge the assistance and advice given to us by Dr. A. S. McFarlane of the National Institute for Medical Research who supplied the labelled albumin and carried out the subsequent estimations of plasma and urine radioactivity,

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The following cases were also demonstrated:

Coronary Occlusion Following Thoracic Radiotherapy, Two Cases.—H. E. S. PEARSON, M.D., M.R.C.P.
Nephrocalcinosis.—Mr. J. LOEB (for Mr. N. E. STIDOLPH).
? Giant Cyst of Liver.—Dr. A. BLOOM.
Choledochus Cyst.—Mr. W. W. DAVEY.
Tricuspid Incompetence with Saphena Varix.—Dr. H. E. S. PEARSON.
Venous Hum in Hepatic Cirrhosis.—Dr. K. C. ROBINSON.
Calcinosis Circumscripta.—Dr. A. L. JACOBS.
Sacro-coccygeal Chordoma.—Mr. P. T. SAVAGE.

OTHER DEMONSTRATIONS

Radiographs of Lesions of the Colon.—Dr. G. OSBORNE.
"Boilable" Camera.—Mr. W. W. DAVEY.
Gastrectomy in the Aged.—Mr. Davey's Team.
Gastro-enterological Unit—Analysis of Operations (1950–1957).—Mr. H. COLLINSON and Mr. S. L. STRANGE (for Mr. W. W. DAVEY and Dr. T. St. M. NORRIS).
Pathological Specimens with Clinical Histories.—Mr. P. T. SAVAGE.
Identity Quiz.—Mr. J. P. WILLIAMS.

[This Meeting will be continued in Golden Jubilee issue, October 1957]

United Services Section

President—Sir CECIL WAKELEY, Bt., K.B.E., C.B., F.R.C.S.

[*March* 7, 1957]

Spontaneous Pneumothorax in the Royal Navy

By Surgeon Commander J. M. CLIFF, M.B., B.Chir., M.R.C.P., R.N.

DURING the last thirty years a large number of series of cases of spontaneous pneumothorax have been reported from various parts of the world and the increasing number of such reports indicates that the condition can no longer be regarded as rare although Perry considered it as "comparatively rare" as late as 1939. There is no doubt that this apparent increasing incidence is due to improved diagnosis, both in the use of radiology and awareness of the condition, as in Perry's (1939) 85 cases where only 26 were recorded in the first seven years against 59 in the second period of seven years. Blackford (1939) noted an incidence of one per thousand male students at the University of Virginia while Schneider and Reissman (1945) found that one in five hundred men examined for military service in the United States gave a verified history of spontaneous pneumothorax.

Kjaergaard (1932) had a clear conception of the condition when he included every case "that appears without demonstrable cause in healthy persons in whom tuberculosis cannot be demonstrated, either by examination of the sputum, by auscultation or by X-ray examination, and in whom the lesion is not accompanied by fever or by pleural effusion".

The material for this investigation was drawn from the admissions to the three Home Port Naval Hospitals at Chatham, Haslar and Plymouth during the years 1943 to 1953 inclusive. During the war years the number of admissions was far in excess of normal and while those joining the Service either voluntarily or for National Service were of the age groups normally serving in the Royal Navy they were supplemented by pensioners and retired officers over the age of 40; there is therefore some bias towards the older age groups in 1943–1946 inclusive. During the eleven-year period under review there are records of the admission of 163 patients suffering from or subsequently found to have a spontaneous pneumothorax; only 3 were female.

Hospital admissions give some idea of the incidence of a disease but few statistics have been published for this condition, and the figures for civil and Service hospitals are not strictly comparable on account of the particular age group and predominance of males in the Armed Forces, the greater tendency to admit Service patients to hospital where the problems of accommodation of the sick in Ships and Establishments often do not permit nursing or even observation, and the fact that Servicemen are selected fit men (Tables I and II).

TABLE I.—ADMISSIONS OF CASES OF SPONTANEOUS PNEUMOTHORAX TO ROYAL NAVAL HOSPITALS

Year	Total No. of admissions	No. of cases of spontaneous pneumothorax	Rate per 1,000 admissions
1943	40,748	20	0·49
1944	40,058	14	0·35
1945	41,788	22	0·53
1946	30,824	17	0·55
1947	20,990	16	0·77
1948	18,729	11	0·59
1949	18,791	9	0·48
1950	17,278	10	0·58
1951	19,402	9	0·46
1952	18,968	13	0·68
1953	20,389	22	1·08
	Totals 287,965	163	0·57

TABLE II.—ADMISSION RATES FOR SPONTANEOUS PNEUMOTHORAX

Author	Period	Source	No. of cases	Rate per thousand admissions for all causes
Perry (1939)	1924–1937	London Hospital	85	0·6
Cohen and Kinsman (1946)	1941–1944	U.S. Army Hospitals	41	0·22
Du Bose, Price and Guilfoil (1953)	1946–1952	Veterans Administration Hospital	75	0·02
Jones and Lyons (1954)	1949–1953	U.S. Naval Hospital Philadelphia	70 (60 analysed)	1·0
This series	1943–1953	Royal Naval Hospitals	163	0·57

Age and sex distribution.—The age of patients prone to spontaneous pneumothorax is shown to be low in all reports, and in civil practice many authors have substantiated West's (1884) observation that the young adult male is particularly prone (Table III). No adequate

TABLE III.—AGE INCIDENCE OF SPONTANEOUS PNEUMOTHORAX

Author	Source	Age range	Average age	0–10 years	10–20 years	20–30 years	30–40 years	40–50 years	50–60 years	60 years old and upwards
Kjaergaard (1932)	Denmark	5–49	—	1	5	22	14	9	—	—
Perry (1939)	London Hospital	—	—	3	11	33	16	11	7	4
Ornstein and Lercher (1942)	Out-patient Private Practice U.S.A.	15–56	28	—	9	23	20	1	2	—
Schneider and Reissman (1945)	U.S.A.	16–35	—	—	23	63	14	—	—	—
Hyde and Hyde (1948)	U.S.A.	18–62	—	—	4	30	13	10	4	2
Myerson (1948)	Boston City Hospital	3–53	27	1	7	17	5	5	1	—
Du Bose, Price and Guilfoil (1953)	Veterans Administration Hospital	19–79	32	—	1	48	2	2	8	2
Jones and Lyons (1954)	U.S.N. Hospital Philadelphia	17–71	—	—	5	41	7	2	4	1
Total				5 (1%)	65 (12%)	277 (51%)	117 (22%)	40 (7%)	26 (5%)	9 (2%)
This series	Royal Navy	18–60	25	—	45 (27%)	90 (55%)	20 (12%)	4 (3%)	4 (3%)	—

theory has been advanced to explain this observation; it has been suggested (Wilson, 937) that there is an innate sex-linked tendency but a more probable reason is that emphysem tous blebs are more likely to develop in the sex which plays all sports and performs fe s of strength in which the intrapleural pressure is built up against a closed glottis (Ornstei and Lercher, 1942).

Physique.—Wilson (1937) noted that all his 11 Yale University students were sing arly tall and lean while Norris (1940) observed that two-thirds of his patients were 10- lb. underweight and Hyde and Hyde (1948) reported that almost all their 63 patients were thin and underweight. Wilson (1937) argued that it is the tall thin young man with low diaphragm and a predominantly diaphragmatic type of breathing who is more like to concentrate tension on the apices of the lungs, but the opposite argument may well be used since the well-built youth is more likely to take part in strenuous exercise and ther fore overdistend the apices of the lungs which are unsupported by the thoracic cage.

It was not possible to assess the physique of the patients in this series accurately from their medical records but there were available the weights of 128 patients and the average weight of the 127 males was 141·2 lb. (Table IV).

TABLE IV.—WEIGHTS OF PATIENTS IN THIS SERIES

Weight (lb.)	110–120	121–130	131–140	141–150	151–160	161–170	171–
Number of cases	11	17	41	25	25	3	5

Family history of spontaneous pneumothorax.—A familial occurrence has occasionally been observed in this condition, Willis (1937) noting it in a brother and sister, Bachmann (1940) in a father and daughter, Brock (1948) reporting 2 patients whose near relatives had had pneumothoraces, and Young (1936) mentioning 2 patients in the same family who developed a pneumothorax while straining at stool; similarly Atwood (1926) observed the condition in a father and son and Rottenberg and Golden (1949) in 2 brothers. It has been suggested that the cause might be hereditary lung cysts in all these familial cases but this condition is rare and Perry (1939) did not feel that there was sufficient evidence for such a diagnosis, pointing out that there was no indication that the condition was transmitted as a Mendelian dominant as in congenital cystic disease of the kidney. There were no familial cases in this series.

Previous history of chest disease.—A previous history of pulmonary disease other than spontaneous pneumothorax was uncommon in this series, 157 (96%) admitting to no such history; of the remaining 6, 3 were asthmatics, 1 had had pleurisy, another pneumonia and the sixth a contralateral pleural effusion.

Emphysema is often considered an unusual causative factor since it is rare in the young (except in asthmatics) and the blebs do not tend to become overdistended with air because they communicate with the surrounding lung tissue, but Perry (1939) found that 20 (91%) of his patients over the age of 40 had clinical, radiological and spirometric evidence of emphysema. In this series the 5 (3·1%) patients with radiological signs of unilateral or generalized emphysema were aged 23, 23, 31, 45 and 55; it was not possible to determine the cause of the unilateral emphysema in the 2 younger patients, 1 not being traced and the other symptom-free nine years later.

The presence of respiratory tract infection at the time of onset of the spontaneous pneumothorax.—Leach (1945) found that 18 (14%) of his patients had an upper respiratory infection and 13 had a cough but in only one did the pneumothorax occur during a bout of coughing. In this series there was a history of such an infection in 18 cases (11%) but the month of admission to hospital does not suggest that this condition is more likely to occur when these infections are most common (Table V).

TABLE V.—MONTH OF ONSET OF PNEUMOTHORAX IN THIS SERIES

Month	Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.
Number of cases	14	12	12	12	13	16	17	15	14	13	14	10

(No record in one patient.)

Activity at onset of the spontaneous pneumothorax.—The relation between physical exertion and the onset of a spontaneous pneumothorax is of considerable interest both physiologically and from a medico-legal aspect, the latter problem being well demonstrated by 13 (22·4%) of Ornstein and Lercher's (1942) patients being industrial compensation cases. Kjaergaard (1932) found no history of preceding physical exertion in 78·7% of the episodes in his report, 16% occurring while the patient was in bed; similarly 4 (6·3%) of Hyde and Hyde's (1948) patients were wakened by symptoms of a pneumothorax and Jones and Lyons (1954) found that 11 (13·3%) of their patients were asleep or just rising. In this series the activity of the patient at the time of onset of the pneumothorax was recorded in 100 cases; 36 were at rest or asleep, 48 were carrying out mild exercise and 16 were taking strenuous exercise. There is therefore no close relationship between physical activity and the onset of a pneumothorax but it remains possible that exertion plays an occasional part.

Asymptomatic spontaneous pneumothorax.—The accidental finding of a pneumothorax at routine chest X-ray is not unusual; Kjaergaard (1932) noted 2 such patients, 5 of Wilson's (1937) 11 cases were detected in this way and Schneider and Reissman (1945) found that 5% of their 100 cases were asymptomatic. In this series 5 men were found to have a pneumothorax at their annual mass miniature radiograph but only one was completely symptom-free, the remainder admitting to cough, chest pain or dyspnœa on exertion, on direct questioning.

Lung involved in this attack of spontaneous pneumothorax.—In this series there were 80 right-sided attacks while 82 involved the left side, a ratio of 0·97:1; in 1 patient there

was a bilateral partial pneumothorax. In 1,001 cases from the literature 529 were right-sided, 453 left-sided and 19 bilateral, alternating or unspecified (Table VI) but there is

TABLE VI.—LUNG INVOLVED IN PNEUMOTHORAX

Author	No. of right pneumothorax	No. of left pneumothorax	No. bilateral, alternating or unknown
Enneking (1923)	73	66	3
Le Wald (1926)	5	5	—
Olbrechts (1930)	4	7	—
Kjaergaard (1932)	33	17	1
Biesenthal and Snyder (1932)	8	4	—
Wilson (1937)	5	6	—
Kirshner (1938)	10	9	1
Perry (1939)	35	48	2
Van Ordstrand (1940)	4	4	1
Ornstein and Lercher (1942)	25	16	—
Pease, Stener and Chapman (1944)	2	5	—
Leach (1945)	76	50	3
Schneider and Reissman (1945)	55	44	1
Cohen and Kinsman (1946)	21	18	—
Niehaus (1947)	15	9	—
Hyde and Hyde (1948)	31	32	—
Rottenberg and Golden (1949)	47	44	6
Du Bose, Price and Guilfoil (1953)	51	39	—
Jones and Lyons (1954)	29	30	1
Total	529 (52·8%)	453 (45·3%)	19 (1·9%)
This series	80 (49·1%)	82 (50·3%)	1 (0·6%)

some evidence that the left side is more often involved when there is a concurrent mediastinal emphysema.

Recurrence of pneumothorax.—Recurrence is frequent at some later date, often in the absence of any evident predisposing cause, and many patients are instructed to lead quiet lives; they are advised not to close the glottis, or to avoid high altitudes or heavy lifting, yet these restrictions seem unnecessary since relapses may well occur while the patient is at rest and much avoidable invalidism may be encouraged. The relapse rate varies from 4·7% observed by Perry (1939) to 29·8% reported by Ornstein and Lercher (1942) with an average of about 20%; the relapse may be in the contralateral lung, as in 20% of Hyde and Hyde's (1948) and 35% of Ornstein and Lercher's (1942) patients. Schneider and Reissman (1945) found that only 10% recurred if two years had elapsed but Rottenberg and Golden (1949) noted the average time between attacks to be nearly two years although 15 (62·5%) of their cases had their relapse within a year (Table VII). 20 (12·3%) patients in this series

TABLE VII.—RECURRENCE RATE OF SPONTANEOUS PNEUMOTHORAX

Author	No. of patients	No. with recurrence	% recurrence
Wood (1931)	71	15	21
Kjaergaard (1932)	51	7	14
Perry (1939)	85	4	4·7
Ornstein and Lercher (1942)	58	17	29·3
Schneider and Reissman (1945)	100	19	19
Cohen and Kinsman (1946)	39	4	10
Hyde and Hyde (1948)	63	12	19
Myerson (1948)	21	3	14·3
Rottenberg and Golden (1949)	97	24	25
Du Bose, Price and Guilfoil (1953)	75	22	30
Jones and Lyons (1954)	60	8	13·3
Total	720	135	18·7
This series	116	14	12·12

(NOTE: the figures from the literature are not strictly comparable with those in this investigation since some authors do not state the period of observation which was from one to eleven years in this series.)

gave a verified history of previous pneumothorax, 12 (7·4%) having had single ipsilateral attacks, 4 (2·4%) two or more ipsilateral attacks, 2 (1·2%) one or more contralateral attacks, while the side of the previous attack was unknown in 2.

Degree of collapse of lung.—Estimates of the degree of collapse vary with the observer and radiological technique and therefore both Leach (1945) and Rottenberg and Golden (1949) divided their cases into only two groups, less than or more than 50% collapse; minimal collapse may not be detected unless radiographs are taken in full expiration and the technique is superlative. In this series the pneumothorax was reported as partial in 97 (59·5%) and complete in 65 (39·9%), while in 1 it was bilateral and partial (Table VIII).

TABLE VIII.—DEGREE OF COLLAPSE OF LUNG

Author	No. in series	Inadequate records	No. remaining	Less than 50% collapse	More than 50% collapse	Bilateral
Leach (1945)	126	32	94	56	38	—
Rottenberg and Golden (1949)	97	9	88	57	31	—
This series	163	—	163	97	65	1
Total	386	41	345	210 (61%)	134 (39%)	1

Presence of adhesions in the pneumothorax radiographs.—The importance of adhesions which prevent further collapse of lung has been stressed in the American literature on account of the greater incidence of subsequent active pulmonary tuberculosis in these patients but they are a group self-selected for the development of pulmonary tuberculosis, the adhesions often being due to a previous tuberculous pleurisy. None of the 6 (9·8%) patients noted to have adhesions by Kjaergaard (1932) developed pulmonary tuberculosis but this did happen to all 3 (5·2%) of Ornstein and Lercher's (1942) cases; similarly Cohen and Kinsman (1946) had 5 (13%) cases with adhesions, 2 having no lung lesion after expansion, 2 inactive minimal tuberculosis and 1 active disease. In this series adhesions were noted at the time of the pneumothorax in 8 (5%) patients but none of the 4 patients followed up for two to nine years developed active pulmonary tuberculosis.

Presence of a simultaneous pleural effusion.—Small effusions are frequent, rapidly absorbed and of no significance and in his definition of pneumothorax simplex Kjaergaard (1932) allowed a trace of fluid in the costophrenic angle so long as it could not be detected clinically; when fluid rises above the level of the diaphragm a hæmopneumothorax or a tuberculous effusion is almost certainly present. In a collected series of cases from the literature a small effusion was present in 31·5% (Table IX) but it was only present in 17·8% of the cases in

TABLE IX.—THE PRESENCE OF A PLEURAL EFFUSION IN SPONTANEOUS PNEUMOTHORAX

Author	No. of attacks in series	No fluid	Fluid in the costo-phrenic angle	Fluid up to the diaphragm	Fluid above the diaphragm
Palmer and Taft (1931)	5	3	1	—	1 (due to blood)
Kjaergaard (1932)	61	49	10	—	2 (due to blood)
Wilson (1937)	11	10	1	—	—
Beatty (1938)	8	5	3	—	—
Kirshner (1938)	20	18	1	—	1 (due to blood)
Ornstein and Lercher (1942)	58	36	22	—	—
Pease, Stener and Chapman (1944)	7	4	3	—	—
Cohen and Kinsman (1946)	39	25	10	—	4 (two due to tuberculosis)
Hyde and Hyde (1948)	63	40	19	2	2 (due to blood)
Rottenberg and Golden (1949)	97	48	46	—	3 (due to blood)
Total	369	238 (64%)	116 (32%)	2 (0·5%)	13 (3·5%)
This series	163	132 (81%)	29 (17·8%)	—	2 (due to blood) (1·2%)

this report; the reason for the disparity of these figures is not clear but it is possible that Service patients are admitted to hospital earlier than in civil life and the chest radiographed before fluid has formed. In one patient in this series the trace of fluid was aspirated and found to be clear, containing 96% lymphocytes.

Presence of fever.—A low-grade fever is often noted in the first week, as in 11% of Hyde and Hyde's (1948) patients, but a temperature repeatedly above 99·6°F. indicates either a tuberculous effusion or a hæmopneumothorax and it is significant that the two of Cohen

and Kinsman's (1946) 39 patients to have fever were both found to have active pulmonary tuberculosis. Temperature charts had been preserved in 66 cases in this series; 14 (21·2%) showed a fever of 99–100°F. for less than a week, while there was no recorded fever in 52 (78·8%).

Laboratory investigations.—Little useful information is obtained from routine investigation of the erythrocyte sedimentation rate (E.S.R.), the white cell count, sputum examination for tubercle bacilli or the tuberculin skin test in spontaneous pneumothorax. Jones and Lyons (1954) found a normal E.S.R. in all 60 cases except one who had pulmonary tuberculosis while Hyde and Hyde (1948) noted that a slightly raised E.S.R. or white cell count was not of diagnostic value. In this series the E.S.R. was normal in 100 (97·1%) of the 103 patients examined and the fact that it was 18, 23 and 25 mm. in one hour in the remaining 3 did not prove useful in the ultimate prognosis, each patient making an uneventful recovery and remaining well for one to ten years; similarly the blood picture was normal in the 49 patients examined and the sputum repeatedly negative for tubercle bacilli in all 67 examined.

A negative tuberculin skin reaction is strong evidence against a tuberculous ætiology for the pneumothorax and there are limited reports in the literature that about half are positive in the absence of active pulmonary tuberculosis (Table X). In this investigation 5 out of 9 patients showed a positive reaction.

TABLE X.—RESULTS OF TUBERCULIN TESTS

Author	No. of cases in series	No. tuberculin tested	Positive	Negative	Doubtful
Kjaergaard (1932)	51	22	12	9	1
Leggett, Myers and Levine (1934)	19	15	7	8	—
Ylvisaker, Kiessling and Kirkland (1940)	17	13	8	5	—
Norris (1940)	25	15	8	7	—
Cohen and Kinsman (1946)	39	12	6	6	—
Jones and Lyons (1954)	60	42	21	21	—
Total	211	119 (56·4%)	62 (52·1%)	56 (47·1%)	1 (0·8%)

Mediastinal emphysema.—Many ingenious theories have been put forward to explain the unmistakable physical sign of a clicking pneumothorax but no experimental evidence was forthcoming until Macklin (1939) showed that over-inflation of the lung of a cat ruptured alveoli causing pulmonary interstitial emphysema, subcutaneous emphysema in the neck and often a concurrent pneumothorax, the air passing to the mediastinum via the vascular sheaths and not by the bronchial sheaths. Scadding and Wood (1939) separated two groups of cases with transitory noises over the præcordium; in the first a chiefly systolic clicking sound always indicated that a left pneumothorax was present while, in the second, churning, crunching or crackling sounds in systole and diastole occurred in mediastinal emphysema, both sorts of sound being found when a pneumothorax was present in association with mediastinal emphysema.

There are a number of case reports in the literature of a left-sided pneumothorax in the presence of mediastinal emphysema (Wolferth and Wood, 1930; McGuire and Bean, 1939; Miller, 1944; Hamman, 1937, 1939) and in the only possible case of a right-sided clicking pneumothorax (Black, 1948) the sound was not observed clinically. In the present series there was radiological evidence of mediastinal emphysema in 2 patients; in both there was a left-sided pneumothorax and an audible and palpable clicking noise was heard over the præcordium.

Air travel.—Air travel may prove dangerous in the removal of patients with a pneumothorax to special treatment centres on account of the expansion of the air in the pleural space when the barometric pressure falls. In this series a large lung cyst ruptured while a man aged 20 was flying as a passenger and he was in immediate respiratory distress while a second patient became increasingly breathless when he was flown to England from the Mediterranean before the lung had completely expanded after a pneumothorax.

Treatment.—Treatment was symptomatic until there was evidence of considerable re-expansion. Air was aspirated from the chest in 16 (9·8%) cases (in 9 for the relief of tension, and in 7 to hasten expansion).

The potential danger of the development of a contralateral pneumothorax and the economic loss from the prolonged sickness under conservative treatment have led to continuous intrapleural suction being advised in order to obtain early expansion of the collapsed lung and Jones and Lyons (1954) employed this method in 15 (25%) of their patients

where the lung had not shown any evidence of expansion after five to seven days on conservative treatment. There is a danger of sepsis with empyema formation, as in one case in this investigation.

Time for expansion of the collapsed lung.—Leach (1945) found that those with less than 50% collapse took about nineteen days to expand while the remainder took about forty-eight days and Cohen and Kinsman (1946) reported an average stay of their Service patients in hospital of forty-one days; in civil practice Schneider and Reissman (1945) observed that their patients were away from work for three to four months and even longer in compensation cases. In this series records are available for 136 patients, the average time for expansion being 39·75 days but there were 8 (4·9%) patients in whom expansion was delayed for 104–171 days. It is in these latter cases that a persistent bronchopleural fistula may be present and Brock (1948) brought to notice the chronic ill-health and marked loss of weight in 46 patients in whom the average duration of the pneumothorax was fifteen months (Table XI).

TABLE XI.—TIME FOR EXPANSION OF LUNG

Time for expansion (days)	Cases No.	Cases %
1–7	5	3·7
8–14	14	10·3
15–21	18	13·2
22–28	20	14·7
29–35	22	16·2
36–42	13	9·5
43–49	9	6·6
50–56	9	6·6
57–63	5	3·7
64–70	5	3·7
71–77	5	3·7
more than 77	11	8·1

Average time for expansion—39·75 days
In 92 cases (68%) lung expanded within six weeks

Death in spontaneous pneumothorax.—Kjaergaard (1932) found references to only 6 deaths in 200 typical cases and in 4 it was due to hæmopneumothorax. Rottenberg and Golden (1949) had two (2·1%) deaths due to tension pneumothorax and several other single cases have been reported. There were no deaths in this series.

Abnormal chest radiograph after expansion.—The final chest radiograph was abnormal in 25 (15·3%) patients; in 13 there were ipsilateral or contralateral calcified lesions, in 6 ipsilateral or contralateral bullæ, in 5 ipsilateral or generalized emphysema and in 1 an apical pleuritis. 5 of these patients had had previous attacks of spontaneous pneumothorax. Cohen and Kinsman (1946) reported similar findings in their Service patients, 17% having minimal inactive lesions.

Final disposal on recovery from the spontaneous pneumothorax.—148 (90·8%) patients returned to full duty while 15 (9·2%) were invalided from the Royal Navy as a direct or indirect result of their spontaneous pneumothorax, the invaliding diagnoses being: inactive pulmonary tuberculosis (4), emphysema (4), recurrent pneumothorax (2), asthma (2), multiple bullæ (1), effort syndrome (1), following pleurodesis (1). In the U.S. Army Air Force Leach (1945) found that 74% returned to duty, 10% were invalided, and the disposal was unknown in the remaining 16% while Cohen and Kinsman (1946) stated that 80% of their men in the U.S. Army were retained and 7% invalided.

THE FOLLOW-UP

119 (73%) of the patients were traced, 3 of whom were dead, leaving 116 (71·2%) for this analysis (Table XII).

TABLE XII.—NO. OF PATIENTS TRACED IN EACH YEAR

Year	1943	1944	1945	1946	1947	1948	1949	1950	1951	1952	1953
No. of cases in original investigation	20	14	22	17	16	11	9	10	9	13	22
No. traced	14	10	14	10	12	8	5	8	7	9	19
Deaths	1	1	—	—	—	—	1	—	—	—	—
No. without recurrence	13	8	13	8	9	7	4	7	6	8	19

Deaths.—One patient died in status asthmaticus at the age of 30, six years after his pneumothorax, and another as the result of a road accident, also six years after his attack;

the third patient died at the age of 59, four years after his pneumothorax and following invaliding on account of emphysema. None of these patients had had a recurrence of his pneumothorax.

Recurrence of pneumothorax.—14 (12·1%) of the patients had had an ipsilateral, contralateral or bilateral recurrence of spontaneous pneumothorax. The relapse rate may therefore be summarized as follows: 20 (12%) of the original 163 patients had had a previous pneumothorax and 14 (12%) of the 116 patients followed up for one to ten years had had a recurrence but this includes only 1 of the original 20 and he was an asthmatic (Table XIII).

TABLE XIII.—PATIENTS WITH RECURRENCE OF PNEUMOTHORAX

Patient	Follow-up in years	Side of relapse	Time interval from first attack	Final chest X-ray after first attack
1	11	Ipsilateral	30 months	Ipsilateral emphysema
2	10	Ipsilateral	3 months	Bilat. calcified lesions
3	10	Ipsilateral	12 months	Normal
		Ipsilateral	30 months	
4	9	Ipsilateral	9 years	Normal
5	8	Contralateral	4½ years	Ipsilateral apical bullæ
6	8	Ipsilateral	2 years	Normal
		Contralateral	6 years	
7	7	Contralateral	25 months	Normal
8	7	Contralateral	7 years	Normal
9	7	Contralateral	7 months	Generalized emphysema
		Ipsilateral	13 months	
		Bilateral	30 months	
10	6	Ipsilateral	3 years	Normal
11	5	Ipsilateral	21 months	Normal
12	4	Contralateral	16 months	Normal
13	3	Contralateral	12 months	Contralateral cysts
14	1	Contralateral	12 months	Generalized emphysema

No recurrence of pneumothorax.—There was no recurrence in 102 (87·9%) of the patients traced (Table XII).

Significance of adhesions in the pneumothorax radiograph.—A follow-up was obtained on 4 of the 8 patients in whom adhesions had previously been observed; 2 had had their pneumothorax in 1945, 1 in 1949 and 1 in 1952 but none had developed pulmonary tuberculosis and only 1 had had a further pneumothorax (contralateral), this patient being known to have generalized emphysema.

Symptoms.—87 (75%) of the patients traced were symptom-free while 29 (25%) attributed their breathlessness on exertion (in 27) or winter bronchitis (in 2) to their spontaneous pneumothorax (Table XIV).

TABLE XIV.—PATIENTS WITH AND WITHOUT SYMPTOMS AT FOLLOW-UP

Year	1943	1944	1945	1946	1947	1948	1949	1950	1951	1952	1953
Number traced	14	10	14	10	12	8	5	8	7	9	19
Symptom-free	11	4	10	7	12	5	4	7	5	7	15
Chest symptoms present	3	6	4	3	—	3	1	1	2	2	4

Chest radiographs.—81 (69·8%) patients had had a normal chest radiograph within the previous two years while 22 (19%) had had no further chest film following recovery from their pneumothorax. 13 (11·2%) patients had abnormal chest X-rays but in 10 (8·6%) the abnormality was known to have been present following expansion of the collapsed lung, leaving 3 (2·6%) who had developed lung lesions during the follow-up period. In one patient a large ipsilateral bulla appeared and lobectomy was performed, another was appealing to the Pneumoconiosis Board for compensation after a chest film had shown some reticulation in both lung fields, while the third had developed open pulmonary tuberculosis. This last patient had had a left spontaneous pneumothorax on three occasions (age 17, 18 and 19), followed by a right-sided attack at the age of 20 with a normal chest film after expansion and he did not develop tuberculosis of the left upper lobe until he was 23 years of age.

Development of pulmonary tuberculosis.—The absence of any relationship between a previous spontaneous pneumothorax and pulmonary tuberculosis is well demonstrated by the long follow-ups in the literature (Table XV) but occasional cases are found where the

TABLE XV.—SERIES IN WHICH PULMONARY TUBERCULOSIS WAS NOT OBSERVED AT FOLLOW-UP

Author	No. followed up	Maximum length of follow-up	Active pulmonary tuberculosis
Biesenthal and Snyder (1932)	12	9 years	Nil
Kirshner (1938)	11	9 years	Nil
Perry (1939)	67	13 years	Nil
Blackford (1939)	14	15 years	Nil
Norris (1940)	23	12 years	Nil
Niehaus (1947)	21	12 years	Nil
Hyde and Hyde (1948)	18	8 years	Nil
Total	166		

presence of pulmonary tuberculosis has no bearing on the ætiology of the pneumothorax. All the 126 men in the U.S. Army Air Force reported by Leach (1945) had been X-rayed before entry or subsequently, yet one had proven active disease, and in a rather similar series from the U.S. Navy Jones and Lyons (1954) found one case of open disease, while Cohen and Kinsman (1946) reported two cases of open pulmonary tuberculosis and seven others with apparently inactive lesions amongst 39 patients in the U.S. Army.

Once a pneumothorax has fulfilled the definition of Kjaergaard (1932) it may be regarded as a benign condition and there is no greater chance of the development of pulmonary tuberculosis than in the average individual in the community. Perry (1939) could find only 6 (2·4%) patients out of a total of about 250 in the literature who developed pulmonary tuberculosis and there was no such case in his series of 85 patients (Table XVI).

TABLE XVI.—DEVELOPMENT OF PULMONARY TUBERCULOSIS AFTER SPONTANEOUS PNEUMOTHORAX

Author	No. of cases followed up	Maximum period of follow-up	No. developing pulmonary tuberculosis	Lung	Time interval
Hamman (1916)	5	6 years	1	Bilateral	34 months (previous alternating pneumothorax with negative Mantoux)
Kjaergaard (1932)	49	20 years	1	Contralateral	3 years (exposed at home)
Leggett, Myers and Levine (1934)	19	Not stated	1	Ipsilateral then contralateral	5 years
Ornstein and Lercher (1942)	40	18 years	3	Not stated	Less than two years; adhesions present
Schneider and Reissman (1945)	65	10 years	1	Contralateral	5 years
Rottenberg and Golden (1949)	97	Not stated	1	Not stated	14 years; adhesions present
This series	116	11 years	1	Contralateral	3 years
Totals	391		9		

Summary.—The case records of 163 patients admitted to the Home Port Naval Hospitals with a spontaneous pneumothorax during the period 1943–1953 inclusive have been reviewed. It is essentially a disease of the young adult male of average physique, associated with no marked constitutional upset, involving either lung equally unless mediastinal emphysema is present when the left lung is more often involved, and it usually absorbs within 6 weeks; physical exertion is not an important precipitating factor but there is a considerable risk of recurrence. 116 (71·2%) of the patients were followed-up for one to eleven years; 3 (1·8%) had died without a recurrence of the pneumothorax, 14 (12·1%) had had further attacks and one (0·9%) had developed contralateral active pulmonary tuberculosis three years after his last pneumothorax.

This investigation confirms that the incidence of pulmonary tuberculosis in patients who have had a spontaneous pneumothorax is no greater than in the general population but it remains important to exclude tuberculosis at the time of occurrence of the pneumothorax.

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BOOK REVIEWS

Medical Ethics. A Guide to Students and Practitioners. Edited by Maurice Davidson, M.A., D.M., B.Ch.Oxon., F.R.C.P. (Pp. viii + 165; illustrated. 20s.) London: Lloyd-Luke (Medical Books) Ltd. 1957.

This book contains a collection of essays dealing with various aspects of the personal relationships met with in practice. Each of the distinguished authors writes in characteristic style on the subject allotted to him, and thus a pleasing variety is afforded.

The functions of the General Medical Council are well outlined by Mr. W. K. Pyke-Lees, and Dr. Clegg gives some wise advice to those doctors who write for the lay press or take part in broadcast or television programmes. Lord Cohen of Birkenhead deals with the doctor-patient relationship with his accustomed clarity, while Sir Heneage Ogilvie writes in plain language about the way in which a doctor should behave towards his colleagues. There is a short but welcome note on "Medicine and the Church" by the Bishop of Durham. Dr. Neville Stafford contributes a chapter on "The Doctor, the Law and the Police" which is excellent but would be almost more appropriate in a textbook on forensic medicine. Dr. Roques delivers wisely conservative judgments on the questions of contraception, therapeutic abortion, sterilization and artificial insemination. There are two useful chapters on clinical subjects—the Management of the Hopeless Case written by Dr. Lindsey Batten, and the Care of the Dying from the pen of Dr. Clifford Hoyle. The last essay is an excellent account of the Hippocratic Oath by Dr. Douglas Guthrie.

We have left for special mention the other two contributors. Professor McCance writes a much-needed chapter on the practice of experimental medicine in which he carefully lays down the safeguards required by therapeutic experiments on the human being. This is the first time we have seen such an essay on this most important subject and we commend it to all workers on the forefront of medicine. Finally the editor of the volume, Dr. Maurice Davidson, has written not only the introductory chapter but also two short essays on difficult subjects—the doctor's responsibility to his own family, and the problem as to what should be told to gravely ill patients. These are written with true humanism, and though the writer says that "judgment, discretion and initiative are not to be taught by rule of thumb" we believe the first two of these can be cultivated by reading such a book as this.

One impression stands out prominently after reading this book, i.e. the immense influence which is still being exerted by the ethical teaching of Hippocrates on the medical profession of to-day. There is much to be said for Dr. Guthrie's plea that some form of the Hippocratic oath should be put before if not taken by every graduate of medicine.

There is some overlapping and on one question we detected difference of opinion. On the question of euthanasia one contributor states that "the doctor must not be the arbiter of life and death" while another comments surprisingly "the law forbids in theory but ignores in practice, thus tacitly accepting the common-sense view that doctors here, as in other spheres, should be protected from the consequences of steps honestly taken in the interests of patients".

De Motu Cordis. Movement of the Heart and Blood in Animals. An Anatomical Essay by William Harvey. Translated by Kenneth J. Franklin. (Pp. xii + 209; illustrated. 17s. 6d.) Published for the Royal College of Physicians of London. Oxford: Blackwell Scientific Publications. 1957.

This excellent translation of the most important medical work ever written will undoubtedly take its place at once as the standard English text. It is written in lucid English, accurate, and altogether a joy to read. Professor Franklin, who is at the same time a distinguished physiologist and classical scholar, has so closely entered into the thought of Harvey that the translation reads as if the work had been primarily written in English. We can give but a few examples of the felicity of translation.

Harvey's resolution to free himself from the bondage of Galen is vividly portrayed. "However, the die has now been cast, and my hope lies in the love of truth and the clear-sightedness of the trained mind." Again, the picture Harvey draws of the failing heart

is wonderfully reproduced—"And while the heart is slowly dying, one can sometimes see it—so to speak—arouse itself and, in reply to two or three auricular beats, produce a single ventricular one slowly and reluctantly and with an effort".

An example of accuracy. At the end of Chapter 9 Harvey wrote—"Ego in illa disquisitione jam sum". This had been rendered by a previous translator—"I shall now discuss this point", and a critical note had been added that Harvey had forgotten to discuss it. Professor Franklin translates correctly and in modern idiom—"I am now busy with that research".

We should like to continue quoting passages which specially appealed to us but shall not do so, for everyone should read the whole book for himself. For the medical student the reading of Harvey's immortal work should be compulsory, and now that this most readable translation is available there is no excuse if he does not become acquainted with it. The reading of the De Motu Cordis is the beginning of physiological wisdom, and every doctor and man of science will enjoy and profit from this beautifully produced volume.

Battle for the Mind. A Physiology of Conversion and Brain-washing. By William Sargant. (Pp. xxiv + 248; illustrated. 25s.) Melbourne, Toronto and London: William Heinemann & Co. Ltd. 1957.

In this book, Dr. William Sargant reiterates his views about abreaction and its reformulation in terms of the Pavlovian conditioned reflex. He goes much farther and considers what he believes to be the close relationship of political indoctrination, religious conversion, and the work of the Freudian psychoanalyst. By political indoctrination he refers to what has been inelegantly called "brain washing". By religious conversion he refers to the rapid and tumultuous changes of heart which apparently occur in some American revivalist meetings after the audience or part of it has been moved almost to the point of frenzy.

The author is at some pains to make it clear that he is not concerned with the validity of any belief but only with the mechanics of its indoctrination. Nevertheless the treatment of the subject matter lacks delicacy of touch and there are passages which might have been written differently without making the author's task more difficult. We read that the Apostle known to most Christians for his wise and moving first epistle to the Corinthians, was acutely excited, transmarginally inhibited, hallucinated, and showed "other inhibitory hysterical manifestations" just outside Damascus. Is not the clinical record in Acts perhaps a little too old and a little too scanty to permit these deductions to be made? True, as Dr. Sargant reminds us, St. Luke was a doctor—but perhaps as a medical journalist, psychiatry may not have been his best subject. When we are told, too, that Chinese Communists have been helped in their task of political conversion by a study of Catholic Missionary methods, one wonders if the author has not over-reached his authority. Certainly it would be interesting to have the views of a Catholic Missionary who has worked in China.

The book is intended to appeal to a wider audience than a purely medical one and "too technical a style has been avoided". This design places difficulties in the path of any writer and perhaps accounts for some loss of accuracy. Thus, "much of our human life consists . . . in the unconscious following of conditioned reflex patterns originally acquired by hard study". How are conditioned reflex patterns studied? Surely the author means acquired habits which become automatic by repeated use. A grown man shaves himself automatically, and even unconsciously but no one would suggest that shaving is a conditioned reflex. Conditioned reflexes as defined and established by Pavlov play a very small part in integrated human behaviour. On pages 7 and 8 there is, included under the term conditioned reflex, a remarkable mixture of what most people would call reflexes, conditioned reflexes, habits, attitudes and sentiments. Precision in the use of language seems to be wholly abandoned when the author, in speaking of E.C.T., explains that John Wesley too was a great believer in electric treatment and possessed a Leyden jar—though he stopped short of convulsions!

A series of illustrations at the centre of the book begins with a Quaker Meeting, goes on to show some excited Negroes, some even more excited revivalists and ends with Rock and Roll, and Wesley in a death cart. The book itself is well written and agreeably produced. It will certainly arouse discussion but it is to be hoped that psychiatrists generally will not be thought to have a *Weltanschauung* as sterilely mechanistic as this. Experience has shown that such a view is still very prevalent and makes the clinician's task needlessly difficult.

Section of Radiology

President—Professor R. McWHIRTER, F.R.C.S.Ed., F.F.R., Hon.F.C.R.A., F.R.S.Ed.

[*November* 16, 1956]

DISCUSSION ON THE RADIATION TREATMENT OF CANCER OF THE ANTRUM AND ETHMOID

Miss Margaret D. Snelling (The Middlesex Hospital, London):

The Treatment of Carcinoma of the Maxillary Antrum and Ethmoid

The method used in the treatment of cases of carcinoma of the maxillary antrum at the Middlesex Hospital was introduced in 1936 and was described by Professor Windeyer in the Skinner lecture of 1943 (Windeyer, 1943, 1944; Windeyer and Wilson, 1955). The whole of the antrum is irradiated with deep X-rays to a dosage of 5,000–5,500 r in five to six weeks. No surgical treatment is given at this stage apart from a biopsy to confirm the diagnosis and, where there is infection, drainage by Caldwell-Luc antrostomy. One month after the completion of the deep X-ray treatment a palatal antrostomy is performed when residual tumour and necrotic debris are removed and a biopsy is taken of any suspicious area. Active growth in the antrum is then treated by an intracavitary radium applicator while any recurrence in the ethmoid region is implanted with radium needles or gold seeds. Since the effect of applicator or implant is necessarily localized to a small volume, this treatment is unsuccessful in cases where there is extensive infiltration and we have in recent years endeavoured to avoid the necessity for this additional irradiation by extending the volume and improving the dosage distribution of the original deep X-ray treatment. As a result of these alterations in our technique the local recurrence rate has diminished considerably.

Table I shows the results obtained in all cases of malignant disease of antrum and/or

TABLE I.—THE RESULTS OF TREATMENT OF CARCINOMA OF MAXILLARY ANTRUM AND ETHMOIDS: 1929–1950

	Total seen	Five-year survival	Full treatment given	Five-year survival
1929–1935	41	3 (7·3%)	33	3 (9·1%)
1936–1940	38	7 (18%)	33	7 (21·2%)
1941–1945	36	8 (22·2%)	27	8 (29·6%)
1946–1950	41	17 (41·5%)	39	17 (43·6%)
Totals				
1929–1950	156	35 (22·4%)	132	35 (26·5%)
1936–1950	115	32 (27·8%)	99	32 (32·3%)

ethmoids seen at the Middlesex Hospital from 1929 to 1950 inclusive. The cases are divided into an early group treated by varied techniques before 1936 and three later groups each of five years, all treated by our present method. The five-year survival rate has improved steadily, rising from 9·1% in *treated* cases before the introduction of the present method to 21·2%, 29·6% and 43·6%. Not all the five-year survivors are free from disease and of the 17 patients in the last group who were alive five years after the first treatment 7 were thought to have disease still present—an apparent cure rate of 25·6%. The result of the more intensive treatment has been, therefore, not only to increase the number of cures but also to increase the average length of life in the failures. An attempt was made to assess the relation between the results of treatment and the histology of the tumour but there were too few cases in each group for any definite conclusions to be drawn except, perhaps, in the case of adenocarcinoma in which the results confirm the impression of apparent cure followed by late recurrence.

Causes of failure.—10 of the 132 cases developed blood-stream metastases and in 11 there was spread to the lymphatic glands. The most important complication by far was the local recurrence which occurred in no less than 35 of the 132 patients—11 times in the antrum and 24 in the orbit or ethmoids.

While recurrence in the antrum is rare with our present technique, recurrence in the orbit and ethmoid remains a very serious problem, which must be overcome if the results are to be further improved. Because of the high incidence of involvement of orbit and ethmoid when the cases are first seen—it was present in 65·8% of the cases treated between 1946 and 1956—these are presumed to be involved in every case, and are therefore included in the first treatment with deep X-rays. The sight of the eye on the side of the growth is thereby endangered but loss of sight is rare except where the orbit is extensively infiltrated or

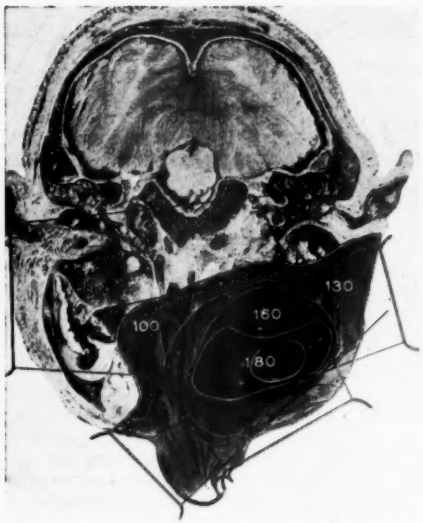


FIG. 1.—Section through centre of antrum—four field deep X-ray treatment (250 kV, H.V.L. 2·4 mm. Cu, F.S.D. 50 cm.).

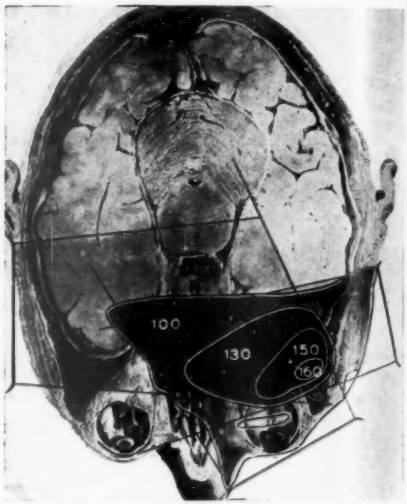


FIG. 2.—Section through orbits and ethmoids showing dosage received by four field treatment as shown in Fig. 1.

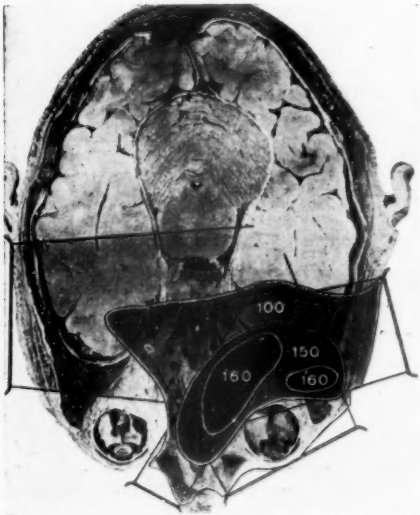


FIG. 3.—Section through orbits and ethmoids showing effect of addition of small field at contralateral inner canthus.

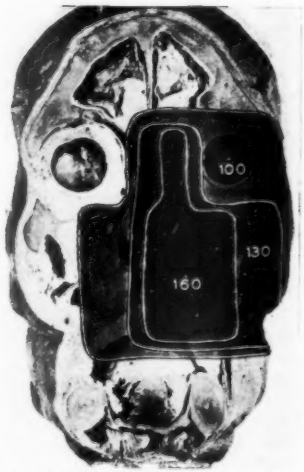


FIG. 4.—Coronal section through antrum and anterior ethmoids showing dosage distribution (treatment as in Figs. 1 and 3).

infected. Every precaution is taken to reduce the irradiation received by the other eye and each case is carefully planned with this object.

Fig. 1 shows a transverse section through the middle of the antrum. Superimposed upon it is the plan and dosage distribution of a four-field deep X-ray treatment. (For this physical chart, as for most of the others, I am indebted to Mr. C. Gregory, now working in the Physics Department at Mount Vernon Hospital.) On the side of the tumour, there are two long fields, 4 or 6 cm. wide, which extend from above the level of the frontal sinus down to below the floor of the antrum; the lateral field is directed medially and forwards and the

anterior field backwards and medially. On the unaffected side, there is an anterior field —usually 4 cm. wide—which extends from the lower margin of the orbit to below the hard palate. This field is directed medially and backwards, the angle depending upon those of the other fields and upon the anatomy of the part.

Since with three fields only the dose is too low posteriorly a lateral field is usually added on the sound side and is directed medially through the back of the normal orbit and antrum to the posterior part of the diseased antrum and orbit. The addition of this field brings the posterior part of the antrum into the high dosage area.

Fig. 2 shows a transverse section through the centre of the orbit. The same four field plan is being used but we are now above the level of the small anterior field on the sound side and the dose received is due to a combination of anterior and lateral fields on the side of the diseased antrum and the lateral field on the sound side. The dosage in most of the orbit and ethmoid region is satisfactory but an inadequate quantity of radiation reaches the anterior ethmoid cells and the antero-medial part of the orbit, which are often infiltrated with growth. A small field, usually 2 cm. wide, is therefore added at the inner canthus on the sound side (Fig. 3) and is so placed and angled as to reduce to the minimum the dose received by the eyeball to be preserved. In this example the medial part of the eyeball receives a maximum dose of 30% of that received by the tumour. The cerebrum also receives little radiation.

Fig. 4 shows a coronal section through the centre of the antrum and anterior part of the eyeball. The antrum, floor of orbit and ethmoids are all seen to be in the high dosage area, while the orbit on the sound side receives relatively little radiation.

I should like to thank Miss Hewland and Mr. Turney of the Art and Photographic Department of The Middlesex Hospital for their help in the preparation of the illustrations in this paper.

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Dr. T. W. Backhouse for Professor B. W. Windeyer (The Middlesex Hospital, London):
The Treatment of Carcinoma of the Maxillary Antrum and Ethmoids by Supervoltage Irradiation

I wish to describe the ideas we have had at Mount Vernon Hospital for the treatment of carcinoma of the maxillary antrum and ethmoids by the supervoltage machines installed there.

The 1,000 curie cobalt^{60} Theratron is designed to be fully rotational; that is, in one plane, it will rotate for 360°, or less, around the patient. It is impossible accurately to rotate in the sagittal or coronal planes, and we are limited in this type of case to a plane parallel to Reid's base line. The large size of the cobalt source, compared to the focal spot of X-ray machines results in an unavoidable and considerable penumbra.

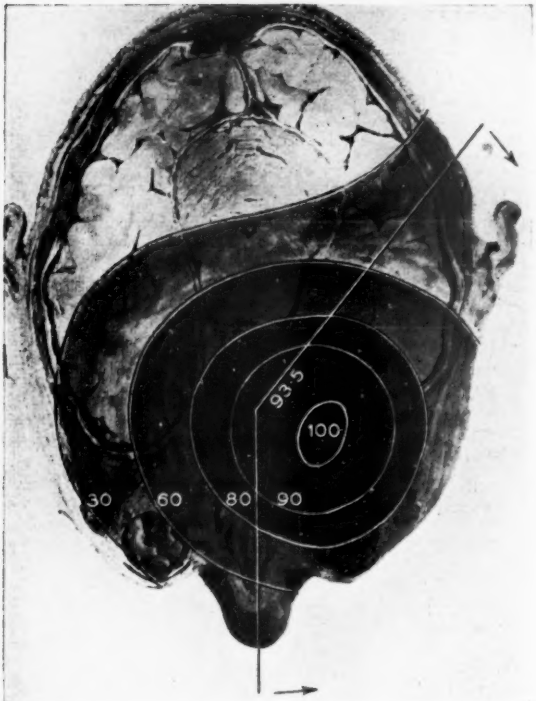
Fig. 1 is a plan of a partial rotation of 140° superimposed on an anatomical specimen to show the distribution of dose. The anterior ethmoidal cells are relatively underdosed and too great a volume of tissue is irradiated. The contralateral eye receives a higher percentage dose, chiefly as transmitted radiation and therefore unavoidable, than we can accept if sight is to be preserved in that eye. Fig. 2 illustrates the coronal distribution.

We have therefore concluded that rotation therapy on the Theratron is unsatisfactory in these cases.

The 4MeV Linear Accelerator has so far been available for fixed field therapy only. It has very sharply defined beams, variable over a wide range of size. Fig. 3 is a typical dosage distribution achieved with two fixed fields, the posterior oblique receiving only half the anterior incident dosage. Fig. 4 confirms that a satisfactory distribution in the anterior and posterior ethmoids and the sphenoidal sinus is not obtained at the expense of the contralateral eye. The mid-line may be transgressed and the eye still spared by using a lead shield 7 cm. thick. A dose rate of 1,200 rads per week to the tumour volume has not led to any serious reaction while the total dose delivered has been of the order of 7,500–8,000 rads.

It is too early to discuss the final results of treatment. Although the Theratron has now been in use for two and a half years, all the cases accepted for treatment were considered untreatable by any other means and yet achieved considerable palliation in the regression of the primary lesion. The Linear Accelerator has only been in use for one year.

I have great pleasure in acknowledging the work of the Physicists at Mount Vernon Hospital, particularly that of Mr. C. Gregory, the help of the Medical Artists at the Middlesex Hospital, and the co-operation of the Photographic Departments of Mount Vernon and the Middlesex Hospitals.



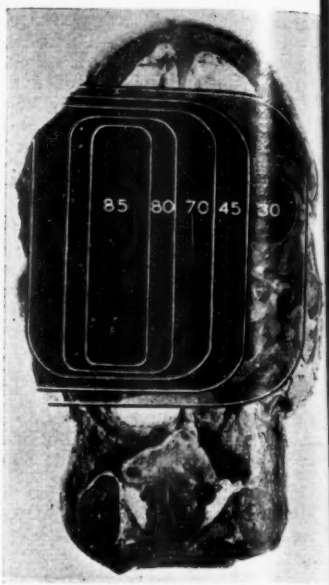


FIG. 2 (above).—*Co^{60} Theratron.* 140 Cycling Rotation dose distribution in coronal plane.

FIG. 1 (left).—*Co^{60} Theratron.* 140 Cycling Rotation dose distribution for irradiation of the antrum.

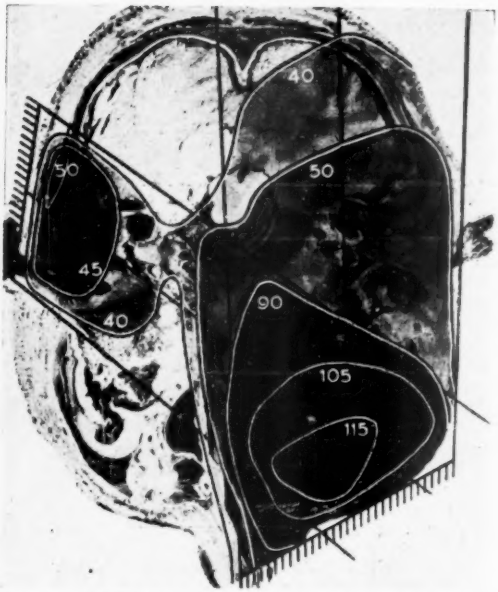


FIG. 3.—4 *MeV Linear Accelerator.* Dose distribution using two fixed fields for irradiation of the antrum.

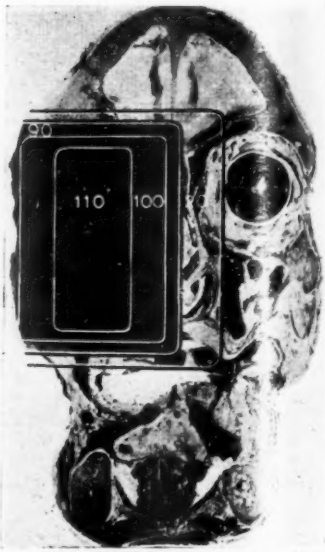
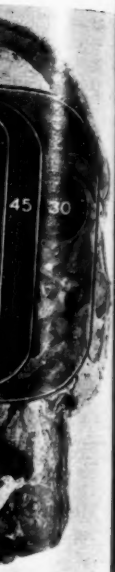
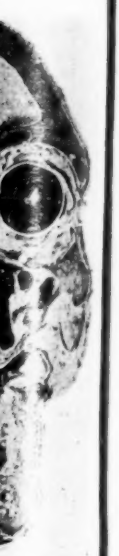


FIG. 4.—4 *MeV Linear Accelerato* Dose distribution in coronal pla



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Dr. V. M. Dalley (Royal Marsden Hospital, London):

Cancer of the Antrum and Ethmoid—Classification and Treatment

The following classification of cancer of the antrum, based on the anatomy of the maxilla, has been developed at the Royal Marsden Hospital:

(1) Zygomatic; (2) Palatine; (3) Frontal; (4) Alveolar.

(1) 16 patients belonged to the zygomatic group and the main feature was pain. Orbital invasion occurred early and trismus was frequently present. Nodes occurred in 4 cases out of 16.

(2) 17 patients belonged to the palatine group where disease has usually spread to the nose and often through the palate into the mouth. The external swelling was in the region of the naso-labial fold. Nodes were never present initially and developed in only one case.

(3) Tumours occurring in the region of the frontal process showed considerable pathological variety. Eye signs and symptoms predominated and epiphora was often present. Nodes were present in 6 cases and widespread metastases in 5 cases.

(4) The alveolar group was the largest, comprising 55 cases. Disease had spread to the mouth either as ulceration of the upper alveolus or as a mass palpable in the upper sulcus. 7 of the squamous group had nodes initially and 7 developed later.

11 of the 130 cases were unclassified either owing to the advanced nature of the disease or to the patient being seen only post-operatively.

At the Royal Marsden Hospital, treatment has always been a combination of radiotherapy and surgery. Preliminary radiotherapy in the form of external radiation is preferred for three reasons:

(1) An extensive tumour is more easily treated by radiotherapy than by surgery.

(2) An impaired blood supply is commonly thought to diminish the radiosensibility of neoplastic tissue.

(3) Subsequent surgery may be more safely restricted, particularly in relation to the orbit, as a result of treatment.

The two exceptions to this policy are (*a*) the very early case where the disease can obviously be completely removed by surgery, and (*b*) the zygomatic group of cases where the presence of cancer and sepsis in the dense bone of the zygomatic arch reduces tumour sensitivity and increases the risk of radionecrosis.

Preliminary drainage operations are not considered necessary. The treated area includes the maxilla, ethmoid, nasal fossa and orbit on the diseased side. 220 kV X-rays are usually used with 3 fields so arranged as to spare the whole of the orbit on the normal side. The usual dosage is 4,500–5,000 r in five to six weeks. Direct corneal shielding is used on the diseased side. Bilateral cataracts occurred in 6 patients and unilateral cataract in 10. 3 of these mature radiation cataracts have been removed and good central vision resulted. 9 exenterations and 8 enucleations of the eye have been performed for disease and 2 eyes have been enucleated by the plastic surgeons but not one eye has been removed for radiation damage. Of those patients who had ocular surgery for disease, only one survives.

Our usual custom if nodes are present initially is to treat with radiotherapy, frequently using teleradium, at the same time as the primary is treated. 3 block dissections were performed in this group and all 3 patients survived five years. Cases treated with radiotherapy alone were usually too advanced for surgery to be performed. The early cases, and recently those with involvement of the zygomatic arch, were treated by surgery with subsequent radiotherapy. Intracavitary radium is not used as the primary method of treatment since by this method one cannot achieve adequate irradiation of ethmoidal or orbital extensions. Its use is restricted to: (i) local recurrence, and (ii) as a post-operative measure when residual disease is present after previous external radiation and has not been entirely removed.

Material and Results.—These are summarized in Tables I and II.

TABLE I.—CANCER OF THE MAXILLARY ANTRUM AND ETHMOID.
Material Seen 1933–1955

ANTRUM		ETHMOID	
Total No. of cases seen	172	Total No. of cases seen	43
Total No. of previously untreated cases	130	Total No. of previously untreated cases	38
Total No. of recurrent cases	39	Total No. of recurrent cases	2
Total No. of cases seen but not treated	3	Total No. of cases seen but not treated	3
Total	172	Total	43

TABLE II.—RESULTS
Previously Untreated Cases

Site	Five-year survivals 1933–1955		Three-year survivals 1933–1955	
Antrum	26/87	30%	36/106	34%
Ethmoid	5/25	20%	11/32	34%

Dr. Robert Gibb (Christie Hospital and Holt Radium Institute, Manchester): *The Treatment of Carcinoma of the Maxillary Antrum and Ethmoid by Radium*

In carcinoma of the maxillary antrum and ethmoid, the problem of treatment of the primary divides itself into three groups: (1) where the antrum alone is involved, (2) where the tumour is limited to the ethmoid, and (3) where both sinuses and the nasal cavity are involved.

The tumours in all these sites taken together, registered at the Christie Hospital from 1940–1950 inclusive, are first reviewed in a general way and thereafter the value of local radium as a treatment method, separately for the early and the late cases, is considered in more detail.

The material available for study is shown in Table I. Tumours of the antrum are certainly the predominating problem and it is perhaps surprising that in only 17 cases were antrum and ethmoid both considered to be involved.

TABLE I.—TUMOURS OF MAXILLARY ANTRUM AND ETHMOID 1940–1950 (inclusive)

Total registered	Antrum ..	276	
	Ethmoid ..	41	
	Antrum/ethmoid	17	
			334
Total treated	Early	105	
	Late	180	
			285
Untreated	Too advanced	35	
	Patient's refusal	4	
	Referred elsewhere	10	
			49

TABLE II.—TUMOURS OF MAXILLARY ANTRUM AND ETHMOID 1940–1950
Pathology

Carcinoma	199
Anaplastic or undifferentiated	13
Reticulo-endothelial	19
Other	19
Unrepresentative, or no section ..	84
	334

The pathological distribution in each of the three groups was similar and they are therefore shown together in Table II. The major group consists of carcinoma and the reticulo-endothelial group will not be further considered here. The "other" group consists of mixed salivary tumours, melanomata and myelomata.

The sex and age distribution shown on Table III, agrees closely with that quoted in Windeyer's (1943) series, with nearly one-third of the patients under 55 years of age.

The staging of these tumours is not very satisfactory, but we have accepted as early for antrum those cases where the estimated tumour volume was not greater than a sphere of 4 cm. in diameter, and where there were no metastases when the patient was first seen. The late group consists of those with a primary tumour of diameter greater than 4 cm., or with metastases already present.

The results of all methods of treatment in the treated cases are shown in Table IV. This shows a reasonable survival rate in the early group, but in the late cases the results are unsatisfactory.

TABLE III.—TUMOURS OF MAXILLARY ANTRUM AND ETHMOID
1940–1950

Distribution		
Sex		% of Total
Male	187	56
Female	147	44
Age		
Under 45		12
45–54		17
55–64		25
65–74		34
75–84		11
85 and over		1

TABLE IV.—TUMOURS OF MAXILLARY ANTRUM AND ETHMOID
1940–1950
Results of Treatment—all methods—five-year Crude Survival

	No. treated	% survival
Early	105	42
Late	180	9
	285	21

The early cases are now considered in more detail. The first, and main, group consists of those early cases with disease confined to the antrum, and treated by means of a radium tube within the tumour mass. The background to this method of treatment is of some importance. Before 1937 a preliminary lateral rhinostomy was done, with removal of the main mass of the tumour, and a radium source enclosed in a sphere of sorbo rubber was introduced into the resulting cavity. Unfortunately the operative mortality from this combined procedure was high—12 patients out of 48 so treated died post-operatively of hæmorrhage and sepsis. The method was clearly too severe for older patients, and those whose general condition was poor. It was therefore decided to use the tumour itself as the radium holder.

The method is well known (Paterson, 1948; Tod, 1948); briefly, the intention is to insert a radium tube as accurately as possible into the centre of the tumour, and to keep it there long enough to deliver the desired dose to the selected volume.

Since the object is to raise this volume to a radiotherapeutic tumour lethal dose, a high central dose must result, and since the bone is involved in the malignant process, sequestration of involved bone is to be expected. If drainage from the antrum is satisfactory following treatment, the reaction is not unduly severe and debris escapes via the hole through which the radium tube was inserted. Occasionally drainage becomes inadequate due to closure of the sinus by healing, or to its blockage by debris, and sepsis within the antrum may lead to severe local pain with later, if the condition is not relieved, a general toxæmia. The re-establishment of drainage, and the clearing out of sequestra, becomes essential in such cases, and is best achieved by removal of half of the palate, although in some cases sequestrectomy through the sinus is sufficient.

The actual radium used is a 25 mg. tube, 2 cm. long, and 0·3 cm. in diameter. It is contained in thin rubber tubing, one end of which is left long. The usual route of insertion is via the canine fossa, but occasionally, where palate or cheek is involved, it may be more satisfactory to go straight through the involved area. The tube is retained in position by stay sutures through the cheek, tied to the long end of the rubber tubing which protrudes into the mouth. The final position of the tube is shown in Fig. 1. The dosage varies, but in



FIG. 1.—Typical position of antrum tube—lateral view.

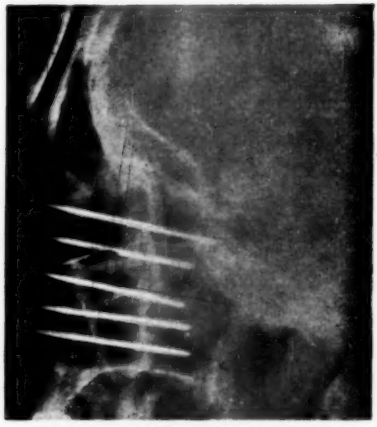


FIG. 2.—Ethmoid implant—lateral view.

general 8,000 r at the surface of a sphere 2 cm. from the radium source, was delivered. Where the tumour was more extensive, this dose was given at 2·25 cm. or at 2·5 cm. from the tube; in some advanced cases additional radon seeds were implanted in the palate, or a plane of radium was inserted in the cheek, to increase the dose in those areas.

The results of this method of treatment in the early antrum cases are shown in Table V.

TABLE V.—TUMOURS OF MAXILLARY ANTRUM—EARLY
Treated—Radium Tube
Five-year Crude Survival Rate

	No. treated	% survival
All cases	60	45%
Histologically proved carcinoma	53	45%

The next group to be considered is ethmoid carcinoma treated by a radium needle implant to the ethmoid area. In principle this has similarities to the antrum tube approach in that the dose is taken 1 cm. from the plane of the needles—and not at 0·5 cm. as in the ordinary single plane implant. This again means a high central dose, with a minimum dose, in seven days, of 6,000 r–8,000 r, at the sides of a slab of tissue and bone 2 cm. in width. The needles are inserted horizontally through bone and tumour, and vertically above each other, in the mid-plane of the growth. 3 mg. needles of 6 cm. total length, 4·5 cm. active length, are used. With the patient supine, a track for the upper needle is made first. Using a twist drill, or some other similar device, of the same diameter as the needle, a hole is made through the skin and nasal bone, 0·75 cm. from the mid-line, at the level of the resting pupils. A dummy needle is then pushed backwards through the ethmoid cells for a distance of 6 cm. in a plane parallel to the sagittal plane of the body, the end of the needle being aimed at a point about two fingerbreadths above the external auditory meatus. The dummy is removed, and the top needle inserted through the channel made for it. The remainder of the implant is then completed, with the needles rather closely together in order to achieve a dose rate of the order of 1,000 r per day at 1 cm. from the plane (Fig. 2).

The results in the ethmoid cases so treated are shown in Table VI. Unfortunately only a fraction of the cases treated in this way were registered as early.

TABLE VI.—TUMOURS LIMITED TO THE ETHMOID
Treated—Ethmoid Implant
Five-year Crude Survival

	No. treated	% survival
Early	5	40%

The next group to be discussed consists of those patients treated by antrum tube combined with ethmoid implant, where both areas were considered to be involved. It has been necessary here to take the early and late cases so treated together, as most were designated late on the principle that when more than one site is involved the condition should be so staged, and even so the numbers are small. In general 8,000 r at 2 cm. from the tube, and 6,000 r at 1 cm. from the implant, were delivered in about seven days (Fig. 3). The results are shown in Table VII.



FIG. 3.—Combined antrum tube and ethmoid implant—lateral view.

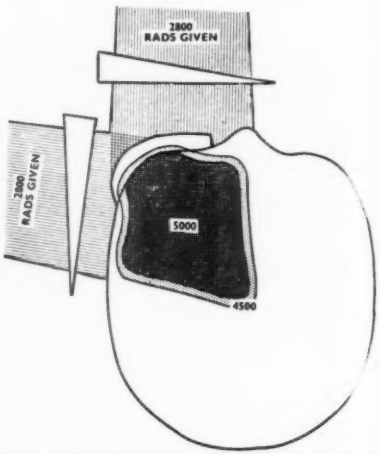


FIG. 4.—Diagram of dose distribution for 2 anterior wedge fields in treatment of carcinoma antrum using 4 MeV radiation. 9 × 8 WCM. field.

TABLE VII—TUMOURS OF ANTRUM/ETHMOID
1940–1950
Treated Antrum Tube and Ethmoid Implant
Five-year Crude Survival

No. treated	% survival
8	50%

In these early groups there were 3 deaths within one month of treatment and the main complication was the expected sequestration of involved bone. In only 16% of the patients, however, was hemi-palatectomy or sequestrectomy necessary. The use of local radium, producing as it does a 5-year survival rate in the three groups of about 40%, appears to be a satisfactory treatment method in reasonable cases.

In the late cases, forming as they do more than half the patients referred, the situation is far less hopeful, and little difference is made to the results either by the site, the pathology, or the type of treatment. The detailed figures are shown in Table VIII. It is of interest that

TABLE VIII.—TUMOURS OF ANTRUM AND ETHMOID
1940–1950
Late Cases Only
Five-year Crude Survival Rate

	No.	% survival
Total Maxillary Antrum	144	8
Antrum tube only	45	7
Antrum (Histologically proved carcinoma)	91	8
Total Ethmoid	24	8
Ethmoid (Histologically proved carcinoma)	16	6
Total Antrum/Ethmoid	12	36

the five-year survival of all cases having block dissection of the neck for secondary nodes was also 7%. Apart from the antrum/ethmoid group, in which the staging may well be fallacious, as mentioned previously, and which includes some cases treated by tube and implant, advanced cancer in these sites is in the category of lung and œsophagus, so far as curability is concerned. Where the lesion is greater than 4 cm. in diameter, antral tube is certainly no better than any other method of treatment, and the only likelihood of improving the salvage is by producing a better X-ray technique. We have found conventional beam directed X-ray therapy to be unsatisfactory, and in view of this a number of patients with advanced lesions, considered to be beyond the scope of local radium, have been treated, since 1951, by a wedge field technique, using 250 kV radiation. This consisted of an anterior pair of wedge fields backed up by a single non-wedge field from behind. The tumour dose was 4,500 r or 5,000 r in three weeks, and 8 out of 17 patients treated are well at two years after treatment. This is certainly promising and worth persevering with, but it is too early to say how the ultimate result will compare with previous methods. It is certainly unlikely to be worse.

On the strength of this initial success, a series of advanced cases is now being treated by an anterior pair of wedge fields on the 4 MeV Linear Accelerator. This lends itself admirably to the use of wedges, as the dose distribution diagram suggests (Fig. 4), and although I would not substitute it at the moment for the radium approach in the early case, it may well improve considerably the results in the more advanced case, and in time, enter into competition with radium as a treatment method for the early.

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Mr. C. P. Wilson (The Middlesex Hospital, London):

There is a natural tendency to emphasize the results of treatment and this emphasis is directed primarily towards the percentage of five-year cures or survivals; although the previous speakers have shown steadily improving results we must beware of adopting an attitude of complacency.

A 60% failure rate does not sound as good as a 40% cure rate and yet the incentive to progress must be in the investigation of failures rather than in the analysis of successes. The main factors emerging from an analysis of the failures suggest that direction of spread

and localization of growths are considered in too narrow terms. In a few cases it is possible to talk of growth localized to the alveolar region, or the palate or antero-lateral wall, but in the majority one should think of the antra and ethmoids as one entity and not as two separate regions. [Mr. Wilson then showed two slides to emphasize this point.]

Fig. 1 showing the extent of spread of growths when cases first presented for treatment is a

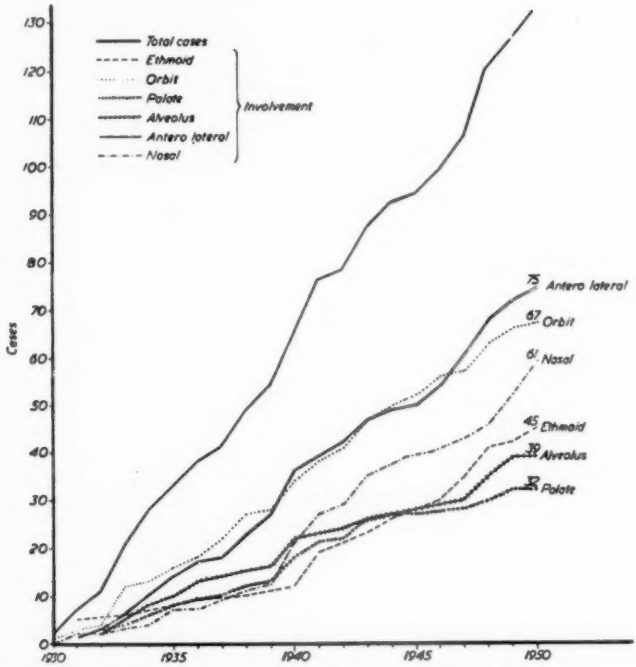


FIG. 1.—Malignant disease of antrum and ethmoid. Extent of disease before treatment.

composite graph. The top line represents the total number of cases seen. The other lines represent the cases in which antero-lateral wall, orbit, nasal wall, ethmoid, alveolus and palate respectively were clinically involved in the spread of the tumour. They add up to very nearly three times the total number of cases. In other words, on first examination, spread had been on the average in three directions outside the antral cavity and antral walls. This extensive spread has made it evident, as stressed by Miss Snelling, that the conception of the volume of tissue to be covered in the original planning has in the past been far too conservative and must be revised very drastically if the whole of the tissue likely to be involved in the disease is to be included in the area of primary effective radiation.

A margin of cover of some 50% more than would appear to be necessary as the result of clinical investigation should be considered and from what has been said it would appear that my radiological colleagues are fully aware of this and in agreement with it.

From the surgical aspect I have in general performed an intra-oral palatal antrostomy with exenteration of the whole ethmoidal region back to the sphenoidal sinus except in cases which were limited to the alveolar regions or the antero-lateral wall or palate. Occasionally this was modified by using a type of Moure's incision if the floor of orbit was obviously involved and sometimes I have gone on to interference with the orbit.

I have rarely practised exenteration of the orbit except in cases of recurrent tumours where it should obviously have been done at the original operation but in which I have not had the courage to advise it because the sight in the eye involved was not impaired.

If it is felt that the radiological cover should be more extensive and complete than that hitherto given then the subsequent surgical exposure must follow suit as far as practicable.

Instead of intra-oral palatal antrostomy being the routine operation the surgeon should consider whether it is not really an operation to be used only in those cases limited to alveolus or antero-lateral wall or palate.

In many other cases where the antro-ethmoidal angle is involved the cheek must be turned aside and the whole of the inner wall and floor of the orbit removed. In those cases where there is at any stage clinical evidence of involvement of the orbital tissues, as shown by proptosis or other form of ocular displacement, exenteration of the orbit must be accepted as the logical form of surgical help, although I doubt if one could, in practice, justify destruction of an eye with normal vision.

If, as I believe is now the case, a logical and determined effort is made to irradiate effectively the whole of the affected area then the subsequent surgical intervention must be sufficient to expose that area as far as is technically possible.

[*February* 15, 1957]

Renal Arteriography in Hypertension

By C. J. HODSON, M.R.C.P., F.F.R., D.M.R.E.

Deputy Director Radiological Department, University College Hospital, London

SOME five years ago when we started investigating the potentialities of radiology in the study of renal changes associated with hypertension our preliminary survey suggested various lines of investigation. One of these was the demonstration by means of arteriography of arterial changes in such kidneys and to this end it was necessary to establish (*a*) what such arterial changes might be, and (*b*) how far they might be defined by means of renal arteriography *in vivo*. This contribution is a brief outline of some of the positive results which have derived from this study.

To define the arterial changes we carried out an extensive investigation of the arterial trees of normal and abnormal kidneys of all kinds using the injection of post-mortem and excised specimens with radio-opaque material and subsequent radiographic examination as our method. At the same time we evolved a radiographic technique to define as far as possible the renal arterial and capillary circulation *in vivo*, carrying out aortography by means of catheterization of a femoral artery, and exposing X-ray films at the rate of one a second, with the radiographic factors adjusted so as to give maximum detail of the renal arterial tree.

Generalized renal arterial changes associated with hypertension.—Injection of a number of specimens showed that the changes which occur in hypertension are largely those due to degeneration of the walls of the arterial tree. They consist of (1) tortuosity of the finer branches of the arterial tree, (2) diminution in the number of interlobular vessels and arterioles, (3) diminution in the distance between the zone of the arcuate vessels and the surface of the kidney, i.e. a narrowing of the true renal cortex.

In the normal arterial tree tortuosity of the vessels is conspicuous by its absence. When early degenerative changes are present the first sign is tortuosity of the branches at the level of the arcuate vessels with a diminution in the number of twigs. In the more advanced cases these changes are accentuated, there being tortuosity of the interlobar vessels and sometimes of the main branches of the renal arteries with again further diminution in the number of peripheral twigs and a decrease in the thickness of the renal cortex.

Comparing these findings with the results obtained by renal aortography, tortuosity affecting the main branches, the interlobar branches and, in a good film, the arcuate vessels might be defined. As well, the thickness of the renal cortex can be shown during the capillary or "cortical blush" phase, but the diminution in the number of interlobular vessels is beyond the power of definition *in vivo* at the moment. In any case it appears that renal arteriography as a means of defining the generalized vascular changes occurring in arteriosclerosis is not likely to be of any great practical value although it certainly may give some evidence in doubtful cases. Renal biopsy appears likely to be an easier and more accurate means of determining these changes during life.

Localized changes.—In those cases of hypertension where the disease is not diffuse but is localized to a part of the kidneys or to part of one kidney the underlying pathological condition is usually localized chronic pyelonephritis, or, in a small minority of cases, a lesion of the main renal artery. Other rare conditions may be unilateral hydronephrosis or some form of obstruction to the urinary tract. I intend to deal only with the first two groups of cases.

Localized pyelonephritis.—The structural change in the kidney which can be assessable radiographically is a coarse localized scarring, either atrophy or fibrosis or both, of a relatively

large segment of the kidney substance. This is almost always associated with expansion of the adjacent calyx and is thus represented on the film by a marked localized diminution in thickness of the renal substance with a localized depression of the outline and with "clubbing" of the calyx. This lesion is readily recognizable in an intravenous pyelogram providing the exposure factors are adjusted to demonstrate the renal outlines.

In an early case in which this defect was present (Fig. 1) it was considered likely that these



A B

FIG. 1.—Localized chronic pyelonephritis. Injected specimen. A shows the marked narrowing of renal substance. B, the contracted tissue round the upper calyx appears to be supplied by a very small separate polar branch of the renal artery suggesting that its cause might originally have been a vascular lesion.



FIG. 2.—Localized chronic pyelonephritis. "Cortical blush" phase of aortography showing irregularity of outline of lower pole with areas showing cortical blush interspaced with contracted "ischæmic" areas.

contracted areas might be associated with a demonstrable abnormality of a branch of the renal artery. Further cases have not directly supported this idea, or, if such an arterial change has been present, it has been overlaid in the radiographic picture by neighbouring vessels. Arteriography can help in the demonstration of this condition during the "cortical blush" phase of the arteriographic cycle when the scarred region stands out sharply against the normal renal cortex which is rendered more opaque by the contrast medium (Fig. 2). The use of renal arteriography to this end is of very limited value, as experience has shown that these lesions can be diagnosed very readily by intravenous pyelography. Aortography should certainly not be regarded as a routine procedure in this group. 3 cases illustrating the value of arteriography in localized pyelonephritis were demonstrated by slides. In each case aortography added very little to the assessment of the case by means of excretion pyelography. In each case there was a smaller renal artery on the affected side and the areas of scarring were shown to alternate with areas of good cortical vascularization. These results were shown to compare faithfully with the injected kidney after surgical removal (Fig. 3A, B, C, D).

Lesions of the main renal artery.—It is in the small but important group of cases where hypertension develops following a lesion of the main renal artery that arteriography comes into its own. The lesion may be thrombosis or embolism, intimal thickening or atheromatous degeneration, aneurysm or pressure from extrinsic causes. It recalls the experimental pioneer work of Goldblatt (1937) in which a temporary rise in blood pressure in experimental animals was obtained by narrowing one, and a permanent rise by narrowing

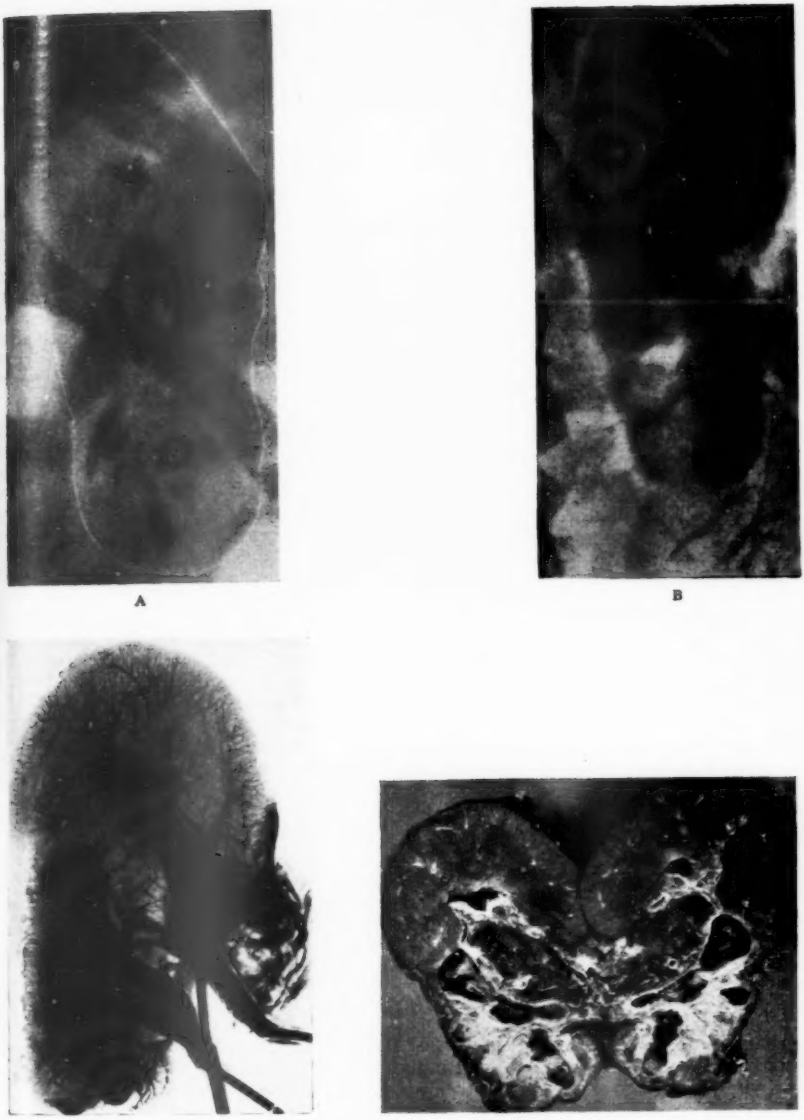


FIG. 3.—Localized chronic pyelonephritis: A, Excretory pyelogram. B, Aortogram—cortical blush phase. C, Injected surgical specimen. D, Surgical specimen; showing value of pyelogram in diagnosis.

both renal arteries. Examples of this group of cases have been described in increasing numbers in recent years, particularly in American literature, and in which nephrectomy (Thompson and Smithwick, 1952), thrombectomy (Freeman *et al.* 1954), or by-passing of the lesion by means of arterial grafts (Poutasse *et al.*, 1956) has resulted in relief of hypertension.

The changes in the affected kidney vary from a slight diminution in size, Howard *et al.* (1954), with almost normal histology, to the classical changes of complete or partial

infarction. Radiographically the main finding is a decrease in size of the kidney as a whole, or, in the case of partial infarction, of a portion of the kidney which corresponds to the size of the vessel affected. On intravenous pyelography there may be no appreciable change or a complete absence of excretion on this side.

Arteriography is probably the most efficient way of investigating this type of lesion. Not only is it the only means of defining its site and extent but it forms the basis of surgical treatment. Asymmetry of the electrolytic contents of urinary specimens by ureteric catheterization gives some indication of a damaged kidney, the main findings being a diminished flow of urine and a lower sodium concentration on the affected side, but I understand these results are not always reliable. It seems likely that renal asymmetry, as shown radiographically, will turn out to be a valuable primary sign in this condition. In our series of cases 2 may fall into this group. One was a man of 36 years with a blood pressure of 180/130 who had been diagnosed elsewhere as a case of right-sided hydronephrosis due to aberrant renal arteries. Of these one had been tied with the result that the lower pole of his kidney had atrophied. The remainder of this kidney looked almost normal at pyelography. On aortography a moderate short-length stenosis of his right renal artery near its origin was shown, and it was thought that this might be producing an ischæmic effect. Hypertension had been present for at least three years and nephrectomy was thought advisable. In fact there was no change in the blood pressure level after operation.

The second was a man of 28 years, with a short history of headaches, a blood pressure of 230/145 and grade II retinal changes. His right kidney was slightly smaller than the left, with a normal calycine pattern on pyelography. An ischæmic kidney was considered. Aortography showed a marked short-length stenosis of his right renal artery just distal to a small branch artery to the upper pole of the kidney. Beyond the stenosis was a marked dilatation. It was considered, however, that ureteric catheter specimens did not support a diagnosis of ischæmic kidney, and so far surgical treatment has not been attempted. In some of these cases the clinical story points to the nature and side of the lesion and the aortogram may then be a conclusive accessory to diagnosis. In others there may be no helpful clinical sign beyond a recent onset of hypertension in a patient, either young or old, in whom there is no family history. If in such a case the difference between the long axes of the two kidneys measured on an X-ray film is over 1·5 cm., and particularly if such asymmetry is supported by demonstrable generalized narrowing of the renal substance on the smaller side, then this is a strong indication of unilateral disease, and if supported by asymmetry on analysis of ureteric specimen, is a reasonable indication for aortography. These statements are based on an analysis of over seven hundred pyelograms in which one of the most striking findings is the symmetry displayed by normal kidneys and in which asymmetry with a normal pelvicalycine pattern on both sides has been associated in a dramatic way with hypertension. The inference that such asymmetry may result from a lesion to the main renal artery is supported by both experimental and published work and by our own experience.

Dangers of aortography in hypertension.—It is too early to be definite as to the dangers of aortography in hypertension. There are the complications inherent in all arterial injections whether by needle or catheter, and presumably when the puncture site is not under one's direct control there is an increased risk of hæmorrhage. Apart from this, there is, as yet, no direct evidence that hypertension carries an increased risk to aortography. In a series of 36 cases only one serious complication occurred in a hypertensive woman of 67 years in whom there was a non-functioning kidney on one side and only the one renal artery had been demonstrated on aortography. Following this examination there was a partial suppression of urine for several days during which the blood urea rose to 348 mg.%. After three weeks she was recovering rapidly with treatment and in six weeks her blood urea was normal again. Details of this case will be published after a follow-up.

Summary

(1) Renal arteriography is likely to be of little value in the general assessment of details of the renal arterial tree in cases of diffuse arteriosclerosis.

(2) The "cortical blush" phase of the arteriogram is of limited value in assessing narrowing and irregularity of the renal cortex in localized chronic pyelonephritis.

(3) In the small group of cases in which lesions of the aorta or main renal arteries are causing hypertension the accurate assessment of the lesion by means of contrast medium offers a major diagnostic weapon.

(4) There may be positive evidence of such a change in an intravenous pyelogram.

(5) Apart from a possible increased tendency to hæmorrhage in cases where the pressure

site is not under one's control aortography in cases of hypertension does not appear, as yet, to carry an added risk.

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Renal Phlebography

By R. E. STEINER, Ch.M., F.F.R.

Director Radiological Department, Hammersmith Hospital, London

RENAL vein thrombosis with or without obstruction of the inferior vena cava, has frequently been reported since its original description by Rayer (1840–41). In the past the condition has been recognized only at necropsy, but with renal phlebography it is now possible to confirm the clinical diagnosis radiologically. Four main clinical types of renal vein obstruction can be recognized:

(i) Thrombosis of the inferior vena cava with secondary involvement of the renal veins.

(ii) Obstruction of the inferior vena cava due to invasion by malignant neoplasm, or to external pressure with renal vein obstruction.

(iii) Primary thrombosis of the renal veins.

(iv) Renal vein thrombosis secondary to primary renal disease.

Thrombosis of the inferior vena cava is usually due to spread of thrombus from the lower limb or pelvic veins.

Primary thrombosis of the renal vein is exceedingly rare except in infancy when the renal blood flow may be reduced due to salt-loss, vomiting, or severe diarrhœa. In a review of 228 cases of renal vein thrombosis by Abeshouse (1945) 40% of the patients were under 2 months old.

Renal vein thrombosis secondary to primary renal disease, such as glomerulo- or pyelonephritis (Schröder, 1926) or renal amyloidosis (Vilk, 1940) can occur as a complication of the renal disorder where the blood flow has been reduced.

The indications for renal phlebography have been defined by Harrison *et al.* (1956), as follows:

In patients with proteinuria with or without œdema in association with the following abnormalities:

(i) Abdominal wall veins with upward blood flow; (ii) unexplained œdema of the lower trunk associated with proteinuria of less severity than occurs in the nephrotic syndrome; (iii) unexplained pulmonary infarction; (iv) malignant disease; (v) single kidney.

THE RADIOLOGICAL INVESTIGATION

There are two main methods of approach: either by injection of contrast medium from below through the saphenous vein using 30 ml. of 70% diodone, or by retrograde injection through a cardiac catheter direct into the renal vein using 15 ml. of 50% diodone.

In the case of caval thrombosis injection from below is unsatisfactory, as it will only demonstrate a blocked vena cava and the collateral circulation; in those patients, retrograde injection through a cardiac catheter which has been threaded under fluoroscopic control through an antecubital vein into the superior vena cava, inferior vena cava, and renal vein, is the method of choice. During the injection a Valsalva manœuvre is carried out to augment retrograde filling of the branches of the vena cava and of the renal veins.

The problem of the clinical aspects of renal vein thrombosis and their radiological investigation, together with a large number of illustrations, has already been published elsewhere (Harrison *et al.*, 1956; and Steiner, 1957).

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Aorto-arteriography in Obliterative Vascular Disease of the Lower Limbs

By T. PHILP, M.B., Ch.B., F.F.R., D.M.R.D.

Radiodiagnostic Department, Royal Infirmary, Edinburgh

AORTO-ARTERIOGRAPHY implies simultaneous examination of the abdominal aorta and the arteries of the lower limbs, and is a procedure which has enjoyed increasing popularity in recent years in the investigation of peripheral vascular disorders. At first the examination tended to be confined to the aorta, its pelvic branches and to one lower limb, but the importance of simultaneous examination of both legs has become increasingly recognized.

The technique of injection commonly employed is as described by dos Santos *et al.* (1929), using a percutaneous translumbar approach. Only one film of the abdominal aorta and its pelvic branches is necessary, but serial films of both lower limbs are taken. A manually-operated cassette tunnel may be used to obtain the latter films, and with one injection it is usually possible to examine all the main arteries below the level of puncture (L.V. 2–3).

The majority of the cases examined can be placed into two categories, those with degenerative disease, that is to say atheroma or atherosclerosis; and those with thrombo-angiitis obliterans, usually comprising a younger age group.

The symptomatology and the effect on the tissues is similar in both these conditions, and they present as intermittent claudication, coldness and numbness of the extremities with diminished or absent pulses, trophic changes and gangrene.



FIG. 1.—Bilateral femoral thrombosis. Symptoms referred to left leg only.

Normal vessels are distinguished by their smooth walls, straight or gently curved course and regular calibre up to the origin of a main branch or until the vessel itself divides. There is an absence of the small tortuous vessels which constitute the collateral circulation. Variations of the normal are not infrequently encountered, e.g. aberrant renal arteries, ectopic kidney, high division of the aorta, short common iliac arteries, &c.

Vessels which are affected by atherosclerosis show tortuosity, diminution of calibre, irregularity of lumen consisting of alternating areas of narrowing, dilatation, and a characteristic ragged outline. The vessel walls may show calcification both on plain radiographs and when filled with contrast medium.

Thrombo-angiitis obliterans affects predominantly the distal arteries, but proximal

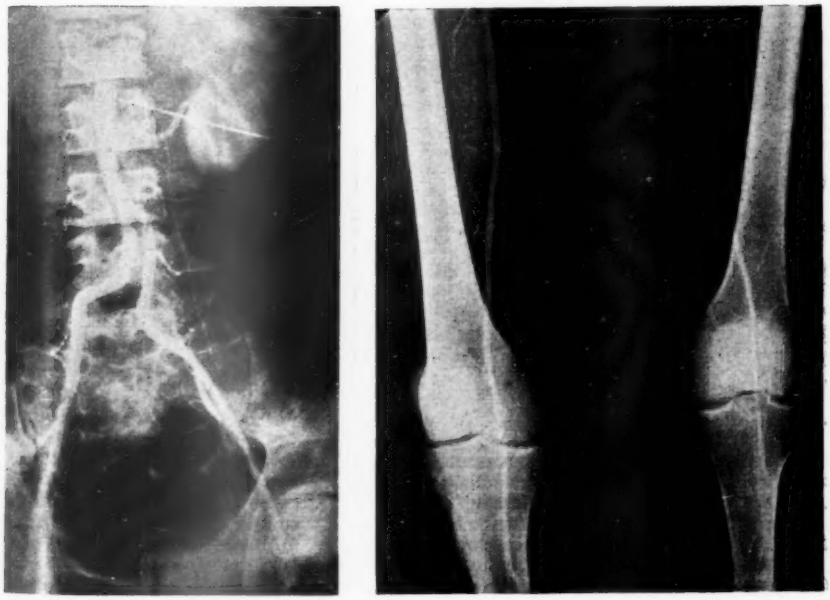
vessels do not escape. In the earlier stages of the disease the vessels retain their smooth walls and there is no tortuosity. It is not uncommon to find both normal and abnormal vessels in the same area, the latter showing only a diminution in calibre with a gradual transition from the normal to the abnormal segment. In the late stages of the disease, areas of dilatation may occur, the vessel walls may become irregular and differentiation from atherosclerosis is often impossible. Mural calcification, absent in the early stages, may also appear later.

Thrombosis of insidious onset is commonly found affecting the peripheral vessels in both atheroma and Buerger's disease, and in the case of the former it may extend to involve the aorta.

By clinical examination it is usually possible to detect the presence of the block, but it is not always easy to define its exact site or its full extent, particularly in the case of high blocks involving the aorta and iliac arteries. Moreover, short blocks are occasionally missed and multiple blocks may be present where only one is suspected.

Though symptoms may be referred to one side only, it is unusual for only one limb to be affected and simultaneous examination of both legs may reveal advanced disease, perhaps even with thrombosis on the contralateral side. Fig. 1 shows bilateral femoral thrombosis though in this case symptoms were referred to the left leg only. Such knowledge gained is of considerable value in planning treatment, and the necessity for subsequent arteriography may be avoided.

Other conditions causing arterial occlusion are comparatively rare and include embolism and tumour involvement of the arterial wall. In Fig. 2A the smooth filling defect in the



A B

FIG. 2.—A, Filling defect in lower abdominal aorta due to tumour involvement. B, Tumour cell embolism causing block at origin of left posterior tibial artery.

left wall of the lower abdominal aorta proved to be due to neoplastic involvement and a block at the origin of the left posterior tibial artery was due to a tumour cell embolus (Fig. 2B).

Numerous complications have been attributed to aortography, due either to the contrast medium or to the technique of injection. The dangers of the former, particularly in high concentrations, are more apparent when injection is made at or above the level of the renal arteries, that is to say, higher than is usual in the investigation of peripheral vascular disorders. Of the others the commonest is extravasation and hæmatoma formation.

Extravasation may occur during the course of injection and be detected on the radiograph but leakage may occur only after removal of the needle. Many such cases have been seen at subsequent sympathectomy.

Recently, Gaylis and Laws (1956) have stressed the danger of dissection following intramural injection and suggest that this complication is more common than has been suspected. Occasionally a small amount of contrast may be injected into the wall of the aorta and remain localized to the level of the puncture.

Direct injection into one renal artery rarely occurs but occasionally the majority of the contrast may enter the renal arteries if the puncture is at the same level. Similarly an excessive amount of contrast may be directed into an aberrant vessel or into a lumbar artery. Fig. 3 shows an excessive amount of contrast in the right testicular artery due to the point of the needle lying adjacent to the origin of this vessel.



FIG. 3.—Excessive contrast in right testicular artery.



FIG. 4.—Small air emboli in branches of the left profunda femoris artery.

Reviewing complications following aortography, McAfee and Willson (1956) state that although it is possible to introduce air directly into the aorta by the injection, no actual cases are known. Any air remaining in connexions between the aortic needle and the syringe or injection apparatus is liable to produce such emboli which will show as small filling defects with convex upper and lower margins (Fig. 4).

Recent reports suggest that the early claims for radical surgery may have to be modified (Szilagyi *et al.*, 1956), and operative procedures may, in future, be limited to the larger vessels, particularly the iliac arteries and the aorta itself. The most important prognostic factors remain the severity and the extent of the obliterative disease, and it appears evident that the radiological investigation will still have an important part to play in diagnosis, and in the planning of subsequent treatment.

I should like to acknowledge my appreciation of the co-operation of my surgical colleagues in this work and for access to clinical records.

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Section of Anæsthetics

President—KATHARINE G. LLOYD-WILLIAMS, C.B.E., M.D., F.F.A.R.C.S.

[*January* 4, 1957]

DISCUSSION ON ANÆSTHESIA FOR OBSTETRICS: AN EVALUATION OF GENERAL AND REGIONAL METHODS [*Abridged*]

Dr. O. P. Dinnick: *Some Aspects of General Anæsthesia*

Speed of induction, certainty of effect and the ability to relax the uterus when necessary, are among the reasons why general anæsthesia is indicated for many major obstetrical procedures; in addition it is more suited to the temperament of many patients and obstetricians than are regional analgesic methods. These are powerful arguments, but general anæsthesia for obstetrics cannot be advocated without considering its most serious complication—the risk of maternal death from inhalation of vomitus.

Hingson in America and Parker in this country have both drawn attention to this very real hazard; their figures are in surprising agreement, with an estimate that there is one death from this cause in approximately 34,000–39,000 deliveries. Parker has noted the difficulty of converting these figures into terms of deaths relative to the number of anæsthetics, as distinct from the number of deliveries, but some attempt must be made to do this.

From the Ministry of Health Report for 1954 giving the results of their Hospital Anæsthetic enquiry, it may be calculated that the number of obstetric operations in the Health Service hospitals under general anæsthesia is approximately 67,600 per annum or 15·6% of the 432,000 hospital deliveries. A further 19,000 operations (4·4% of deliveries) are performed using regional analgesic methods. This figure of 15·6% is an overall figure, but it does not seem to be an unreasonable estimate. The anæsthetic rate is obviously much higher in certain special obstetric units, for example, at the Middlesex until recently it was 60%. (These figures bear no relationship to those for the provision of general analgesia earlier in labour.) If we assume, and we must remember that this is not proven, that all of Parker's estimated 20 fatalities per year from inhalation of vomit occur in these 67,600 hospital anæsthetics, then there is one death in 3,380 obstetric general anæsthetics. On the other hand, this figure of 1 in 3,380 renders less valid the assumption that all these cases occur in hospital; for Parker's figure of no deaths in 3,048 domiciliary forceps cases, on which he partially bases his conclusion, is thus not statistically significant.

This estimate of 1 death in 3,380 anæsthetics, though indeed serious, nevertheless compares favourably with the overall anæsthetic mortality in most series reported from general surgical services (e.g. Beecher and Todd, 1954). Moreover it is not difficult to find higher (Greenhill, 1947) death-rates—including death from inhalation of vomit—where spinal analgesia has been employed (Hingson and Hellman, 1956). However, little purpose is served by arguing on the basis of these figures because it is generally accepted that the skill of the anæsthetist is of greater importance than the method he employs.

The figure of 20 deaths per annum must remain but an estimate until the Ministry of Health announces the full results of its confidential inquiry into obstetric deaths. Meanwhile it must be considered in relation to the recently published figures in the Registrar-General's 1953 Statistical Review which do not entirely support the quoted statement (*Brit. med. J.*, 1956) that anæsthesia is the commonest cause of death in operative obstetrics, at any rate in this country, where there are 150 deaths listed as "complications of delivery". It must never be forgotten that many of the mothers at risk have been admitted to hospital for delivery because of some anticipated obstetric abnormality, which might if untreated lead to an equally fatal result. Even if the 20 deaths due to inhaled vomitus are concealed in the figures of 33 for antepartum hæmorrhage, and 24 for postpartum hæmorrhage, plus 27 for retained placenta and 24 for prolonged labour among other causes, they will still not amount to the most common cause of death.

In trying to view this hazard in its proper perspective, I do not minimize its gravity, nor seek to deny that it should be largely preventable.

The risk of aspiration of vomit, though increased in obstetric cases (La Salvia and Steffen, 1956) is not peculiar to this specialty; it looms large in all emergency and pædiatric surgery, and indeed is an ever-present hazard in every anæsthetic, and is the largest single cause of anæsthetic deaths in this country (Edwards *et al.*, 1956). In cold surgical cases every effort is made to ensure that the patient's stomach is empty before operation. Nevertheless, vomiting sometimes occurs, often from simple disregard of instructions, and not infrequently from delayed gastric emptying due to apprehension. Ruthless logic suggests that a large-bore stomach tube should be passed before every anæsthetic, not just in cases where vomiting is anticipated; but even this precaution is not necessarily effective in the presence of an undiagnosed œsophageal pouch, or in some cases of hiatus hernia. Moreover, it is an

unacceptable, time-consuming, and often unenforceable precaution, as is the alternative suggestion of passing a cuffed endotracheal tube under local analgesia. Another suggested solution is the induction of vomiting by apomorphine pre-operatively (Holmes, 1956). Apart from the humanitarian objections to this, there is some doubt as to its effectiveness. For example, Hersheshon and Brubaker (1947) administered apomorphine 1/50 grain two-hourly, as a sedative in labour, and stressed that not all their patients vomited. Moreover, apomorphine has been known to produce circulatory collapse as in a case recently described by Parr (1956) and this author, while underlining its potential dangers, also mentions that it is not successful in inducing vomiting after every administration. We must, therefore, reject all these approaches for routine use, and though a considerable proportion of women vomit during labour, and thereby reduce the risk to themselves, *we can never assume that such an episode—no matter how induced—guarantees an empty stomach.*

Hiatus hernia is being increasingly recognized and is not uncommon in pregnancy; for example, 9% in a series examined by Mixson and Woloshin (1956). Regurgitation of acid stomach contents is a common accompaniment of this abnormality, and has been suggested as an explanation for some cases of heartburn of pregnancy. Indeed a hiatus hernia was found in 27% of women with this symptom in their series, and the incidence was considerably greater—70%—in a small series of cases examined at the Middlesex Hospital (Whiteside, 1956).

It may well be that this mechanism accounts for some of the unexpected regurgitations which are encountered; indeed, regurgitation and aspiration has been known to occur in normal sleep with this condition (Hadley, 1956). Antacid tablets give symptomatic relief of heartburn, and it seems possible that their administration in labour, at least to mothers with a dyspeptic history, would provide an effective prophylaxis for the serious consequences of aspirating acid described by Mendelson (1946).

It has also been suggested by Coleman and Day (1956) that all obstetric cases, because of their well-known tendency to vomit, should be considered and anæsthetized in the same fashion as a case of intestinal obstruction. Such a conclusion seems too sweeping, is not practical, and overlooks the distinction between regurgitation and vomiting; moreover, they experienced trouble in two cases out of a hundred.

One of the perhaps unexpected findings in the Association of Anæsthetists report (Edwards *et al.*, 1956) was that fluid vomitus was a much more serious hazard than the solid undigested meal; the inhaled material being fluid in at least 92 cases out of the 110 reported fatalities. This finding is perhaps less surprising in the light of O'Mullane's elucidation of the mechanism of regurgitation; and of the extreme rapidity of its occurrence. This is certainly in line with clinical experience, for I cannot recall a regurgitation of solids, out of many sordid episodes—save perhaps in cases with an obstruction, or a pouch of the gullet. Vomiting on the other hand is a co-ordinated reflex act, which gives warning of its imminence.

In parenthesis, one might draw attention to an implication of O'Mullane's (1954) work which has perhaps not been sufficiently considered—namely, the importance of ensuring that the œsophagus as well as the stomach is empty in cases of intestinal obstruction. I have been experimenting with a double-bore ballooned tube to meet this need, but as yet my results are inconclusive.

It would seem therefore that the cases most at risk are not those who have just eaten a good meal, but on the contrary, it is the 3–5% of prolonged labours who are the more likely to produce the copious fluid vomit. The evidence of Parker's (1954, 1956) cases supports this contention, and indeed this is the common experience with these mothers. It is now generally agreed that "keeping up the mother's strength" in labour is a policy to be applied with the strictest caution by the oral route. Any meal should be of a bland low-residue type, and above all, strong hypertonic glucose drinks should be avoided. Again I suggest that cautious medication with antacids is worthy of extended trial.

Though seldom necessary, there should be no hesitation in resorting to intravenous feeding should serious dehydration or acidosis appear in the course of a long labour.

Continuous extradural block has been advocated in these protracted confinements, not only for analgesia and any operative procedure, but also as a treatment for the uterine dysfunction (Johnson, 1954; Johnson and Clayton, 1955; Youngman and Lloyd, 1956; Ball and Chambers, 1956), and this approach seems worthy of further trial.

Nevertheless, there will still be a considerable number of women who will need a general anæsthetic after a prolonged labour. Here the need for obstetric intervention can sometimes be foreseen, and therefore carried out as a planned procedure, and in this small group of cases it does indeed seem reasonable that they should be treated in the same fashion as is an intestinal obstruction. This implies, of course, that there should be available all the ancillary equipment of modern anæsthesia, including a sucker and some form of tilting table for the skilled anæsthetist who wishes to use them. Morton and Wylie (1951) have discussed in great detail the problems associated with this type of anæsthetic, and the technique they recommend for the experienced anæsthetist, of induction and intubation of the patient in the anti-Trendelenburg position is much to be recommended. One of the

hazards of this procedure, namely the risk of inducing circulatory collapse, is less likely to be present in obstetric cases, as the majority of mothers are not dehydrated to a serious extent.

There are two main methods of inducing anæsthesia in this position, either using thiopentone and a relaxant, or by inhalation with cyclopropane followed by a relaxant if necessary. My experience with cases of intestinal obstruction leads me to prefer the inhalation method with cyclopropane (Bourne, 1956) and there seems little doubt of its superiority in obstetric cases; moreover, as I hope to show, there are other arguments against the use of thiopentone. In cases of this kind, the use of thiopentone or large doses of relaxants is particularly to be condemned with the patient horizontal and supine, for no matter how slick the anæsthetist, the regurgitation is often too quick for him.

These major techniques with cuffed tubes cannot, and indeed need not, be applied to every obstetric case, because so frequently anæsthesia is required at extremely short notice, and even when a skilled anæsthetist is available, he may yet not have time for the essential preliminaries to this more complicated technique. Moreover, it is not possible for anatomical reasons to guarantee a rapid intubation in every case, and failure in these circumstances may indeed be serious. If endotracheal intubation is not planned, then anæsthesia must be induced by inhalation methods which have the tremendous advantage that, should any vomiting occur, it is a co-ordinated process of which some seconds' warning is given, and, most important, the protective laryngeal reflexes are still active; but this warning may easily be overlooked, and the protective reflexes stifled, if the facepiece is firmly strapped on with a harness. The anæsthetist must always be alert and prepared to treat this complication effectively should it arise, by gravity, suction, and, if necessary, a relaxant and intubation. Intensive postural drainage of the lungs—perhaps with ether-induced coughing—as soon as possible, is an essential part of this treatment, and one which empties those depths of the lungs beyond the reach of bronchoscopes and suckers. This is surely not too much to ask, for, as has been stated, it is a situation which may be met at any time in any anæsthesia, *and it is submitted that an episode of this kind should never have a fatal outcome in a fit patient.* For example, Davis and Gready (1946) described 45 cases of inhalation of vomit in labour (out of 50,000 cases), of which only 2 died, and then the fatalities were due, they state, to mismanagement.

There is an important implication in the treatment of an episode of this nature during labour, namely that it must take precedence over the obstetric manœuvre. This is not only in the mother's interest, for the temptation to hurry and complete the delivery immediately must be resisted as the child would then probably be born severely hypoxic. It is usually better to wait until the mother's airway is restored, and ample oxygen administered which will reach the child through the umbilical cord, enabling a pink baby to be unhurriedly extracted.

The posture of the patient.—No one would deny that obstetric, and indeed all patients should be in the lateral position during emergence from anæsthesia—be it noted that in at least 30% of the series reported by Hingson, the vomiting took place after the birth of the child. Induction in this position has also much to recommend it and, in domiciliary work, where facilities and manpower are limited, the case for anæsthesia and delivery on the side seems overwhelming. In hospital, where there is, or should be, adequate assistance, a tilting table and a skilled anæsthetist, the situation is not comparable, and under these circumstances the obstetrician's request for the lithotomy position can usually be met.

In view of the traditional advocacy—not mainly by the anæsthetists—of the lateral position, we must ask our obstetric colleagues for a clear enunciation of the relative merits of these two positions for delivery.

It has been argued that it is unduly hazardous to use the lithotomy position when the patient is not intubated, as the associated greatly increased abdominal pressure predisposes to regurgitation, but this reasoning overlooks O'Mullane's observation that the raised abdominal pressure *per se* does not render the cardia incompetent in the absence of obstruction to inspiration. Experience suggests that this practice is less dangerous than would at first appear, and even Parker feels that the case against the lithotomy position in hospital is unproven. There is of course no problem—after induction—if the patient is intubated, but such intubation may not always be possible. We must also weigh the merits of a rapid, adaptable and light anæsthesia, against the slower tempo, deeper and possibly more traumatic anæsthesia with the intubated patient. I would remind those who are in favour of routine intubation, that this policy has yet to be proved over a large series of cases. Hingson and Hellman (1956) intubated but 2 patients in 15,000 deliveries and I, also, usually prefer not to intubate, and rely on the ability to recognize the warning of impending vomiting given with inhalational anæsthesia, and treat that condition promptly, should it occur.

Results.—In justification of this policy, which may appear reactionary, I can only say that this has been the practice at the Middlesex Hospital, where we have had no death from inhalation of vomit in the Maternity department for at least twenty-five years. This period has been chosen partly in an attempt to collect enough cases, partly because it is within memory, and

partly because it covers the period when an anæsthetic machine came into general use in the enlarged department.

I have re-examined the notes and post-mortem records of the earlier deaths, and have excluded the possibility that inhalation of vomit was a contributory cause of a death.

Unfortunately the records are not absolutely complete, so I can only estimate the total number of general anæsthetics at about 9,000. It may be that this is insufficiently precise, but there is no doubt about the post-war records of 5,600 consecutive general anæsthetics without a death, from any cause. However, these figures are easily bettered by Lock and Greiss (1955), who reported 18,868 consecutive obstetric anæsthetics without a death. These workers do not give their morbidity figures; in our 9,734 post-war deliveries we must admit to at least three major aspiration pneumonias, a rate comparable to that of 1 in 2,560 deliveries quoted by Hingson and Hellman.

Thiopentone

Opinion is also divided about the use of thiopentone, which can be considered from three aspects: namely, the effect on the fœtus, the facilitation of the induction of the anæsthesia, and the risk of vomiting. With regard to the effect on the fœtus, the drug is undoubtedly transmitted through the placenta, but differing views have been expressed on how quickly equilibrium is reached. Hellman *et al.* (1944) showed that there was an appreciable concentration of the drug in the fœtal blood after five minutes, but that the maximum concentration was not found until twelve minutes after it was administered to the mother. More recently, McKechnie and Converse (1955) have shown that a considerable amount of the drug may be detected after only 45 seconds, and that equilibrium with the maternal blood levels may be reached in as soon as 3 minutes. Crawford (1956) in this country has again shown that the placenta is no barrier, and claims to have shown that the fœtal blood level falls at the same rate as that in the maternal blood. He therefore suggests, contrary to the recommendations of Hellman and many others, that the longer the interval allowed between the administration of thiopentone and delivery, the lower the fœtal blood level will then have fallen, with therefore less likelihood of respiratory depression. There is much force in this argument; nevertheless, some infants in his series, as in those of McKechnie and Converse, had disproportionately high thiopentone levels many minutes after its administration, and one can only speculate on some possible reasons for this. There may be a variation in the volume of amniotic fluid, placental size or choriodecidual blood pooling; moreover, any estimation of serum thiopentone levels should take into consideration the pH of the blood and the ratio of thiopentone in the free or protein-bound condition (Dundee, 1956). These many possibilities, together with the very variable occurrence of fœtal respiratory depression, all emphasize our lack of precise knowledge in this field. There is also a possibility that the fall in blood pressure after the administration of thiopentone may alter transplacental dynamics, and thus embarrass fœtal oxygenation by the same mechanism as with an inadvertent high regional block.

Two factors, however, are clear; thiopentone is transmitted to the fœtus, and this drug is a powerful respiratory depressant. It seems reasonable, therefore, to limit its use. I am aware that many people have used this drug with satisfactory results, and I have, in the past, used it myself—sometimes as the sole anæsthetic—for Cæsarean sections and forceps deliveries, and while it was usual for the babies to cry lustily on delivery, they tended, not infrequently, to relapse into a stuporous condition shortly after delivery, and to give rise to some anxiety for a few hours. I now restrict its use to a minimal dosage of 100 to 200 mg. for very apprehensive mothers, and then only when there is no suggestion of fœtal distress.

It has also been suggested that thiopentone renders induction smoother, and therefore safer for the mother and fœtus. This may be true in some cases, but it seems to me to overlook the fact that most mothers, either from the exertions of labour, or in "cold" cases from the absence of depressive premedicant drugs, usually have a very active respiratory exchange, which renders an inhalational induction easy and rapid. In any case, most mothers are trained to accept, and indeed look forward to, an inhalation at some stage of their labour, and it is not common to find "the horror of the mask" which is often met with in other fields. Indeed, the ability surreptitiously to convert analgesia to anæsthesia is one of the great advantages of inhalational methods.

The more persuasive argument for the use of thiopentone comes from the obstetricians, especially for an assisted breech delivery in combination with some form of local infiltration when undoubtedly a rapid induction with no struggling is of the greatest importance. It is probable that the risk to the fœtus in these circumstances is relatively unimportant as the cord is probably already compressed, but the hazard to the mother of regurgitation and vomiting is then not inconsiderable. I am aware that one of the most skilled and enthusiastic reporters of breech deliveries (Cox, 1950), with an excellent fœtal salvage rate, advocates thiopentone anæsthesia for the after-coming head, but I believe with Law and Ransom (1954), that inhalational anæsthesia can provide equally satisfactory operating conditions with greater safety for the mother.

Conclusions

It is considered that for many major obstetric manœuvres, general anæsthesia by inhalation remains the method of choice. The available drugs must therefore be briefly reviewed. Cyclopropane has many advantages when a rapid induction is of paramount importance, but its use should be confined to this period, for, in my experience, prolonged cyclopropane anæsthesia is more likely to lead to fœtal depression, as would indeed be expected, as this drug is a powerful respiratory depressant. There was some experimental evidence in favour of this conclusion as long ago as 1939, when Smith found that the concentration of this drug in the fœtal blood was as high as in the mother's, whereas in similar circumstances the nitrous oxide concentration was only half the mother's; and Taylor *et al.* (1951) showed that the delay in reaching full oxygen saturation in the fœtus after delivery was greatest after cyclopropane anæsthesia.

Nitrous oxide then, with oxygen, remains, as in many other fields, the mainstay of obstetric anæsthesia, and where relaxation of the uterus is required, ether, which is least depressing to respiration, seems to possess the fewest disadvantages. In practice, any other vapour which happens to be available on the machine—even CO_2—may be used if necessary to speed the induction, although trilene is best avoided where the mother has already received a lot of pethidine. Vinyl ether has much to recommend it, but has the disadvantage of producing considerable salivation. The newer ethers are as yet unproven, are less predictable, and may cause a fall in B.P. As always, the details of administration depend on the ability of the anæsthetist and his familiarity with the method, remembering that one of his aims is to ensure adequate oxygenation of the fœtus before delivery, and this is most easily done with open circuit anæsthesia.

It certainly does seem reasonable to reduce the numbers of mothers at risk by using the simpler regional methods, and that is indeed our policy now. About 22% of our deliveries including the Cæsarean sections and most of the difficult forceps are done under general anæsthesia, though very few of these are intubated; and a further 35% comprising some outlet forceps, and all the repairs, receive local infiltration, often with inhalational analgesia as well. Pudendal block occupies a middle position, according to the progress of the labour, and the skill and enthusiasm of the obstetrician. But there are other arguments for using local methods, besides that of avoiding the risk of inhaling vomitus.

Pudendal blocks and local infiltration are most valuable techniques for the potential general practitioner, or domiciliary obstetricians, and for those going overseas, and are therefore well suited for use in teaching institutions. The administrative simplification and reduction of demand on a busy anæsthetic service is not to be scorned, and this makes it easier to supply a senior anæsthetist for those general anæsthetic cases where his skill is so needed. This reduction in demand may be considerable, as, for example, at the Middlesex, where 50% of recorded "normal deliveries" have either an episiotomy or small tear to be repaired. Finally, it must not be overlooked that this desirable increased use of local methods is not unconnected with the introduction of that excellent drug lignocaine, and perhaps also hyaluronidase, which render these procedures so very much more effective.

I have not been primarily concerned with domiciliary obstetrics, but in fact many of these recommended methods are equally applicable there; local infiltration, and pudendal block are certainly so, and inhalation N_2O–O_2, ether and cyclopropane in the lateral position with little difficulty. Most of the long labours should be, and usually are, in hospital.

Crawford has made the excellent point that obstetric anæsthesia would be simplified, and the standard raised for the less practised anæsthetist, if the routine anæsthetic for these cases approximated to those given for surgical operations; I agree, but instead of advocating the use of thiopentone in obstetrics, I prefer to use this argument in support of the continued teaching of inhalational methods.

I hope I have succeeded in showing that this "old-fashioned" N_2O–O_2 ether sequence is not used in obstetrics because of habit or tradition. On the contrary it is specifically indicated for its flexibility, its relative innocence to the fœtus, its ability to relax the uterus when required (intravenous ergometrine now renders this a safe procedure), and above all, because with it there is warning of impending vomiting, which, should it occur, does so when the protective reflexes are present.

It may be argued that it is a difficult technique, it is no more so than many others, and is, after all, the fundamental technique of our craft, but this argument turns on the old truth, that no method is better than the person who uses it. No one would deny that for the obstetric case in hospital that person should be a skilled senior anæsthetist; he must always be available.

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Mr. J. S. Tomkinson: *Requirements of the Obstetrician*

I have thought it best to approach the evaluation of general and regional methods of obstetric anæsthesia, from the point of view of the obstetrician, by stating the requirements of an ideal obstetric anæsthetic and then by mentioning the probable anæsthetic of choice for various obstetric procedures.

The first and most important requirement is absolute safety for mother and child.—To achieve this one must consider firstly the dangers of a full stomach to the mother and the steps which may be taken to minimize these and secondly the hazards of hypoxia to the child.

The mother should be instructed regarding diet following the onset of labour. Heavy meals must be avoided. An emetic dose of apomorphine may be considered as a means of emptying the stomach. A tilting bed at the instantaneous control of the anæsthetist has also proved its value.

Concerning the safety of the baby, important work has been published which demonstrates clearly that the risks of hypoxia to the baby are increased markedly after the 40th week of pregnancy (Walker and Turnbull, 1953, *Lancet*, ii, 312). The oxygen supply to the baby may become inadequate for many reasons including damage to the umbilical cord, placental insufficiency, prolonged uterine contraction or defects on the part of the mother in providing an adequate level of oxygen. Any additional hazard causing further anoxia, such as readily occurs during the induction of general anæsthesia, may tip the balance against the baby's survival. When the oxygen saturation in the umbilical vein falls below 30% there will be evidence of fœtal distress including passing of meconium and irregularity or slowing of the fœtal heart.

Walker suggests that the anæsthetic for the delivery of the anoxic fœtus should be spinal, local or caudal, since during the induction period of most general anæsthetics there is a time when the maternal oxygen uptake may be impaired. Similarly it has been pointed out, by many authorities, that regional methods are safer for delivery in many instances where the fœtus *in utero* is at risk, as in maternal diabetes, pre-eclamptic states and fœtal immaturity.

So far we have only mentioned as our requirements the safety of the mother and baby. Often speed of induction may be demanded by the obstetrician and there can be little doubt that here general methods have the advantage.

The length of time for which pain relief is required is an important consideration. No general method of anæsthesia could provide such a long period of pain relief, with equal safety to the mother and baby, as continuous epidural techniques. They are, however, time-consuming, take great skill in administration and are not invariably successful.

The position of the patient for delivery. I am convinced that the lithotomy position is the best to satisfy the demands of the obstetrician for ease of access to the patient, accurate anatomical diagnosis of the position of the baby relative to the maternal pelvis and for maintenance of asepsis. Furthermore, the fœtal heart is easily checked and the patient is in the correct position for the management of the third stage of labour and for the suturing of an episiotomy.

The advantages of *pudendal nerve block* are numerous and it is now widely used by obstetricians. It is almost completely safe for the mother and completely safe for the baby. It has few complications for the mother and none for the baby. It is easy to learn and one can quickly become efficient at the technique. The equipment is easily carried and can be used in hospital or home. The obstetrician is independent of the skilled anæsthetist. The mother is awake and able to co-operate.

In conclusion, the wishes of the patient must be taken into account. I do not consider it advisable to adopt any one method as being satisfactory in all cases but I certainly think that any anæsthetist who is proposing to co-operate in obstetrics should be able to combat the risks inherent in inhalation anæsthesia in pregnancy and labour and should be skilled in the use of regional methods.

Dr. G. C. Steel: I shall attempt to evaluate the known dangers and virtues of regional anæsthesia against the known requirements of the mother, the child and the obstetrician.

I agree with Dr. Dinnick concerning the hazards of spinal anæsthesia: the immediate dangers to the mother and, through her, to the child, of sudden collapse, hypotension and respiratory embarrassment are very real: but they largely arise from abuse of the method and from simple ignorance of the effects of giving a spinal to the full-term woman: an ignorance which happily is disappearing. Headache is on the debit side of the balance sheet, and Rosenbaum *et al.* (1952) give an incidence of 0·7% for the occurrence of chronic adhesive arachnoiditis in patients who had previously had "saddle block anæsthesia". Spinal anæsthesia, however, scores very heavily on the grounds of efficiency: it does its job in that it cuts the afferent stimuli: it gives the surgeon good relaxation: it largely avoids the dangers of vomiting: blood loss is minimal; and, if proper precautions are taken, it has no adverse effect on the child. It is reasonably easy to perform and can be done quickly; it is swift in action; and the likelihood of laryngeal spasm is small. I deprecate the wholesale use of spinal anæsthesia to secure "painless childbirth" in all cases, but where one is presented with an obstetric emergency it may well appear to be the method of choice. In this and many other instances the anæsthetist is wholly justified in employing spinal anæsthesia. The tragedies of continuous caudal analgesia arose from it being used as a routine: and again, as in the case of spinal anæsthesia, from total ignorance of the effect of a sympathetic block. "Total ignorance" is a far greater danger than "total spinal".

The disadvantages and the dangers are also familiar: injury of a blood vessel and possible injection into it; puncture of the dura; hypotension; over-rapid absorption and the possibility of too rapid rise of the drug; together with prolongation of labour, a high forceps rate, and failure of rotation of the occipito-posterior case. It can be technically difficult, and may be more so than is lumbar extradural block. Finally I am always rather unhappy about its proximity to the anus, especially in the case of an indwelling needle.

In its favour its efficiency is very much greater than is generally thought, that is if it is a true caudal. Probably the great majority of so-called "Failed Caudals" were never caudal blocks at all, but had the solution deposited outside the sacrum. Again, caudal block will get to the sacral roots with rather more certainty than if the lumbar epidural route is used. It possesses the other advantages over inhalational anæsthesia that are inherent in regional blocking, and it is outside the theca.

Its therapeutic uses and their particular application to uterine inertia and cervical dystocia have already been described (Galley, 1950; Arthur and Johnson, 1952; Johnson, 1954; Ball and Chambers, 1956; Youngman and Lloyd, 1956). As an alternative approach, the use of the lumbar extradural block for inertia is perfectly feasible and probably preferable to the caudal route. The salient features are: firstly, the extraordinary efficiency of the method: when a woman is having the heightened pain of the ineffective contractions of uterine inertia, it is wholly gratifying to see the change in her facial expression as the block begins to work. She frequently falls asleep; and this is not a stuporous slumber, but one that comes from complete freedom of pain. The next point is its precision: it seems to me to be so much more rational than the random depression of the function of the sensorium. It is the single bullet hitting the target as opposed to the indiscriminate peppering of the barn door with shot. I am a strong convert to the passage of a catheter with a Tuohy needle in the upper lumbar region, an operation which is simple and perfectly painless. While the continuous method is certainly preferable, a single injection of a mixture of Xylocaine 1½% and Nupercaine 1/600 can well give complete relief from pain for up to three hours, by which time the cervix may be dilated, and, if not, the injection can be repeated. Such a block does not usually control the pain of the pressure of the head down on the perineum, but that is a small problem as compared with that of the pain of inertia. The point on which I should like guidance from the obstetrical side is whether or no the blocking of the sacral plexus from the beginning is essential to the success of the method.

Contrary to general opinion, the acquisition of the technique of extradural block demands but a reasonable amount of patience and of application: in return one

acquires something which is of the utmost value in obstetrical anæsthesia. To locate the space I prefer the Dogliotti method. In a small proportion of cases there is said to be an absence of the negative pressure which obviously vitiates the efficacy of the Odoms indicator and of other similar methods. This does not matter so much in the alternative method because, as the needle comes up to the ligamentum flavum, the feeling of resistance increases sharply. As it does so, a correspondingly increased pressure should be exerted by the right thumb pressing on the plunger: this can be quite considerable. When the needle then enters the extradural space, even if there is no actual negative pressure present, the relative difference of resistance is immediately and unmistakably perceptible. Saline is preferable to distilled water for use in the syringe as, when using the latter, the patient may complain of pain at the moment of entering the extradural space. This has also been noted by Lund *et al.* (1956). The sight of fluid dripping back does not necessarily mean that the dura has been punctured: indeed in the very rare case, the injected fluid can spurt out. The injection of the anæsthetic solution must be done really slowly so as to form a local pool, rather than strip its way upwards. Bromage (1954) recommends that for Cæsarean section the pressor drug should be given before the blood pressure falls: with this I agree, but I have noticed that the fall is much smaller when the woman is in labour rather than when an elective section is being done.

The use of epidural block for Cæsarean section was described by Dawkins (1947). It is the method of choice both for mother and child in the "problem Cæsarean", complicated by factors such as cardiac disease, full stomach, prematurity, postmaturity and the like. In the last year at Queen Charlotte's Hospital I have used this method in 10 out of 23 of my cases (44%) and my total personal series for Cæsareans is just over 50 cases, which compares with 100 (Wendl, 1956) and 125 (Ansbro *et al.*, 1952). Gordon *et al.* (1955) have also described a series done with continuous epidurals, and have expressed a preference for Cyclaine to Xylocaine. They quote a failure rate of 5%. I would rate the efficiency of this method as very high. It has the obvious advantages of regional as opposed to general anæsthesia. When it does fail to give perfect freedom from pain I have found that this does not occur during the incision of the skin or of the peritoneum, but at the stretching of the fibres of the lower uterine segment or during the extraction of the head. On one occasion I found that, whereas the patient did not even feel this, she complained of definite pain when the ergometrine was given and the uterus contracted down very markedly. It is perfectly permissible to give the patient a light gas and oxygen at such a time. Sleep only is needed: full oxygenation can be maintained: and the danger of spasm is minimal. The outstandingly good condition of the mother following operation is a most constant feature.

For the baby I consider this the method of choice, especially when there are complicating factors. This is in agreement with the findings of Stewart (1954) and those of Lund (1955), who, in the case of the full-term fœtus, could find no statistical difference in the variations of the infant mortality when done under spinal, balanced or epidural anæsthesia. He found, however, a statistically significant difference in these rates following Cæsarean section when the fœtus was premature, the mortality rate being lower in conduction anæsthesia than in general anæsthesia. The baby delivered under an extradural block cries immediately and continues to cry. The latter point is of particular interest, for, though many methods are praised on the grounds that the baby cries within a short time, a more certain picture would be given if we excluded from those figures those babies who cried at the moment of delivery or on the clamping of the cord, but who thereafter slumped into a relatively stuporous state persisting for several minutes.

My experience of using lumbar extradural block for forceps is very small and confined to difficult cases where I have found it extremely valuable, although one cannot invariably be sure of the solution tracking down to the sacral roots to give perfect cover. Even if the cover is incomplete, nevertheless it does some four-fifths of the task, especially if intra-uterine manipulations are necessary: and again it minimizes danger by cutting the afferents. In this respect Comerford (1956) recommends that puncture should be done between L.3 and 4, or L.4 and 5, with the patient in the left lateral position and with 20 degrees of reverse Trendelenburg tilt; this, he found, gives perfect analgesia from S.5 to D.8 or 10, using 25 c.c. of 1·5% Xylocaine with adrenaline. He further recommends that this method should be used for all forceps deliveries.

There are some real and many imagined disadvantages of extradural nerve block. Firstly it is said to be time-consuming; this drawback is rapidly overcome by familiarity or by the anæsthetist starting his work fifteen minutes in advance. Secondly, Dr. Dinnick has mentioned the failure rate of extradural block. The success rate of any method is in direct proportion to the experience and the enthusiasm of the operator. Mastroianni *et al.* (1955), who passed one catheter into the lumbar extradural space to control the pain of the first stage and another through the sacral hiatus to stop that arising from pressure on the perineum, quote the failure rate of the former as 4% and of the latter as 25%. Foldes *et al.* (1956) state that in 422 cases of extradural blocks 22 instances occurred in which there was

partial failure—a rate of 5·2%. Initially one's failure rate may be 50%; thereafter it drops steadily, and, provided that one keeps in practice, the partial failure rate goes below 5% and the total failure rate between 1% and 2%. Thirdly, hypotension. The danger of a fall in blood pressure lies in the failure of the operator to remember that it is liable to occur. The pressor drug should be drawn up in the syringe before the block is done. I have never had any trouble in restoring it in Cæsarean sections, though my Registrar at the Royal Free Hospital states that on one occasion she found it difficult to restore it before the baby was born (Goetzee, 1956). No ill consequences resulted. Lastly, total spinal analgesia is quoted as a possible danger. I consider this is very unlikely, and in some of those cases which have been so described, respiratory paralysis may have been due to over-rapid injection of a large amount into the extradural space, with the result of its stripping its way up to the upper dorsal and cervical regions.

The danger to the child through the action of the uterus contracting violently under spinal anæsthesia has been mentioned by Macintosh (1949) and by Ward *et al.* (1952). Ruppert (1955–6), however, states that hyperactive disturbances of motility of the uterus which might endanger the child do not result from epidural analgesia. This difference may be of some significance, in view of the more selective action of drugs placed outside the theca instead of inside it.

I have read of one case of mild meningitis following extradural injection, but I have never known myself of any nerve damage following extradural block in obstetrics and gynæcology. As well as anæmia, hypotension and diseases of the central nervous system, I would hold as one of the contra-indications of the use of epidural any marked degree of stretching or distortion of the spine due to the use of the bridge, since I have personal experience of one case of root injury associated with a high extradural block and prolonged use of the bridge.

Too much significance should not be attached to associated disasters. In December 1956 I considered doing a continuous epidural on a case, but decided not to. Eventually the case was delivered with forceps under general anæsthesia. Ten days later she developed incontinence of urine. No fistula was found, and the incontinence, which still persists, is thought to be of neurological origin. The moral is obvious.

It is my practice to teach the Resident Anæsthetists at Queen Charlotte's Hospital and at Chelsea Hospital by doing a large amount of gynæcological operations under extradural nerve block. In the last year at Chelsea 59% of my anæsthetics for hysterectomies have been done with extradural block. Again I would recommend this practice, because, for lower abdominal surgery, I consider it to be the method of choice, particularly in the outstanding protection that it confers on the patient, together with good relaxation and minimal bleeding. I have said briefly that there are difficulties in applying extradural block to every case of forceps. The practice of the residents at Queen Charlotte's Hospital appears to follow along the same lines as those mentioned by Dr. Dinnick. In the last year out of 323 forceps deliveries 282 were done under inhalation alone and 33 were done with an inhalation plus the use of a relaxant. Other methods total 8.

In my opinion, it is essential that every anæsthetist should be able to undertake regional analgesia with that certainty of success which comes from learning the technique and keeping himself in practice. Whilst its outstanding value is high in the field of obstetrical anæsthesia, it cannot be regarded as being solely concerned with this and it is essential that it should form a routine part of postgraduate teaching. Similarly, of mankind, John Donne said "No man is an island intire of it selfe. Every man is a parte of the continent, a peece of the maine".

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Dr. J. M. Holmes: *The Prevention of Inhaled Vomit during Obstetric Anæsthesia*

During labour the stomach continues to secrete a gastric juice of high acid content and in normal labour of even relatively short duration the motility of the stomach is very considerably reduced. This gastric atonia permits the accumulation of large quantities of partially digested food which may be vomited and aspirated into the respiratory passages during general anæsthesia.

Apomorphine hydrochloride has been given intravenously as a pre-anæsthetic emetic to 118 women in labour. The patient is asked to remove her dentures and then 1/40 grain of apomorphine hydrochloride is injected intravenously over 30 seconds from a dry sterile syringe. The needle is left in the vein and the onset of vomiting awaited. On rare occasions it may be necessary to give a further 1/80 grain. After a short period of preliminary nausea the patient vomits profusely within 45 to 90 seconds of beginning the injection and this persists for a further 30 to 60 seconds. The feeling of nausea rapidly disappears as soon as the stomach is completely empty and always within three minutes of beginning to vomit. Atropine sulphate, 1/50 grain is given slowly by intravenous injection through the same needle as soon as vomiting begins and this will rapidly antagonize the slight vagal effects of apomorphine and is also an essential premedication prior to general anæsthesia. The patient is instructed to clear her nasal passages of mucus and, after waiting a few minutes for the atropine to take full effect, general anæsthesia is induced.

During the actual vomiting there is a slight increase in sweating and lacrimation and the pulse-rate rises by 10 to 20 beats per minute. The blood pressure remains unchanged. Occasionally the patient has complained of slight vertigo, which has not persisted for more than a few minutes. There is a marked intestinal hurry and barium meal has reached the cæcum within 5 minutes of taking it by mouth and within 3 minutes of the apomorphine injection. The stomach is therefore emptied not only via the œsophagus but also via the pylorus.

Many patients vomit during the course of their labour and obstetricians have come to accept this as physiologically normal. The apomorphine vomiting which is described does not disturb the patient to any greater extent.

The technique has been used on 118 occasions. 10 patients did not vomit but since they did not vomit during or after the anæsthetic it was assumed that the stomach was already empty. It is believed that the routine adoption of this method would effectively remove the dangers of vomiting and inhalation of gastric contents during obstetric anæsthesia.

Dr. C. J. Massey Dawkins:

If the Tables of Anæsthetic Mortality issued by the Registrar-General are consulted, it will be found that over the last five years, taking the anæsthetics in common use for labour, there were 16 deaths from chloroform, 83 from cyclopropane, 56 from trilene, 106 from nitrous oxide—and none at all from vinyl ether. This is a very remarkable fact and it is unfortunate that the great safety of vinyl ether is not properly appreciated.

It may be argued that vinyl ether is not often administered, but on consulting the explosion survey carried out by the Ministry of Health in the hospitals of England in 1954, it will be found that it was given at least 10,000 times. And as this survey did not cover dental clinics and general practitioner operations where vinyl ether is given much more often than in hospital, the real incidence of use must be at least 20,000 per annum if not much more. An anæsthetic which has been given 20,000 times a year for five years without a fatality is indeed a safe one, and it should be regarded as the anæsthetic of choice in maternity work where it is necessary to anæsthetize the mother.

I would agree with Dr. Steel that epidural block is the ideal method of providing pain-free labour without harm to mother or child and that it should be much more widely used than it is. With regard to pudendal block, American anæsthetists do not claim a success rate of more than 91% and those English anæsthetists with whom I have discussed the method do not claim more than 80% success but I would agree that the method is a very safe one.

Dr. H. R. Youngman:

We teach the junior staff of our obstetric as well as anæsthetic departments to use caudal and pudendal blocks. We invariably add adrenaline to the anæsthetic solution. This does not seem to be universal practice but we regard it as an important safety precaution. Severe toxic reactions have been reported from both kinds of block when it was not used. At Dr. J. A. Lee's suggestion I have recently used amethocaine for epidural analgesia in long obstetric cases; in some each dose has lasted four hours, as compared with two for lignocaine. I find methoxamine an improvement on the other pressor drugs. Its effect is indistinguishable from that of Methedrine except that it does not increase the heart-rate. This suggests that it acts in a more efficient way, and the absence of palpitation is an advantage for the conscious patient.

Section of Comparative Medicine

President—DOUGLAS MCCLEAN, M.B., M.R.C.S.

[*March* 20, 1957]

DISCUSSION ON MAMMARY TUMOURS

Mr. E. Cotchin (Department of Pathology, Royal Veterinary College, London):

Spontaneous Mammary Neoplasms of the Domestic Animals

Neoplasms of the mammary gland are common in the bitch, and form a significant proportion of the less commonly observed tumours of cats, but are of no practical importance in the mare, cow, sow or ewe. There are, in fact, few reports of mammary tumours in the larger domestic animals, and quite large numbers of tumours have been examined by various workers from these species without finding any examples of mammary tumours. Thus Head (1957) informs me that in a series of 116 tumours from horses, 292 from cattle, 106 from sheep and 4 from pigs, no epithelial mammary tumours were found, and only one mesodermal tumour—a mast-cell tumour—in an adult Ayrshire cow, with similar lesions in the supra-mammary, iliac and left prescapular lymph nodes, and the uterine and abdominal walls.

In the *mare*, although few cases of mammary tumour have been reported in recent years, an older report referred to by Feldman (1932) stated that 45 out of the 184 carcinomas found in 39,800 horses slaughtered in Paris abattoirs were in the mamma, and Surmont (1926) apparently had no difficulty in obtaining specimens from the abattoir.

In the *sheep*, Monlux *et al.* (1956), in a series of 66 tumours, found 4 adenocarcinomas which had widespread and peritoneal metastases: although the site of origin was not identifiable, owing to the conditions of slaughter, it was thought that they originated in the urogenital tract or the mammary gland.

In the *sow*, Feldman (1932) found a tumour in the mammary gland, with the histology of a primary adenocarcinoma.

Turning to the *cow*, it has been a matter for comment for a very long time that the cow's udder is hardly ever reported to be affected with cancer, and quite large series of tumours from cattle have been collected which included no such cancer. Thus there was none in the series of 908 bovine tumours examined by Monlux *et al.* (1956) in America and of 1,943 tumours examined by Chandrasekharan Nair and Sastry (1953–54) in India.

This rarity of cancer in the cow's udder is not merely a question of age. Swett *et al.* (1940) made an extensive study of the udders of 313 cows, of which 98 were over 8 years of age, without finding any tumours.

Reports of carcinomas of the cow's udder have been made by Boucek (1906)—only a histopathological description is given; Murray (1908)—the authority of this diagnosis is unchallengeable; Cleland (1908)—this case, from Australia, was considered acceptable by M'Fadyean; Kenny (1942)—the histopathological description of this case is convincing: there was an adenocarcinoma in the left part of the udder, with metastases in the supra-mammary nodes, lungs, bronchial and mediastinal nodes, and liver, and on the peritoneal surface of the diaphragm; Elder *et al.* (1954)—the tumour, in a 3-year-old Aberdeen Angus heifer, is not a typical adenocarcinoma; Poynton (1954–55)—an intraduct carcinoma of the udder is listed as one of the tumours examined in South Australia (it is understood that this case may be reported in detail later).

In these four larger farm animals, then, there is no significant incidence of neoplasms of the mammary gland. In the dog and cat, the situation is quite otherwise. In a series of 3,444 tumours from dogs examined at the Royal Veterinary College since 1940, 840 were from the female genital system, and 694 (20%) of these were from the mammary gland, while of 464 tumours in cats, 44 (just under 10%) were from the mammary gland.

In the *dog*, mammary neoplasms are practically confined to females. They do occasionally occur in male dogs, and it appears, for example (Hoskins *et al.*, 1953, p. 155), that dogs with Sertoli cell tumours of the testis (which have feminizing effects) may sometimes develop mammary tumours, and the writer has recently seen an example of a benign mixed mammary tumour in a dog with an interstitial cell tumour of the testis. In a recent series, the writer has examined mammary tumours from 424 dogs; all but 2 of the animals were entire females—the other 2 were bitches which had been castrated, but not until late in life: one of them, with a benign tumour, two years previously at 8 years of age.

The ages of the affected bitches in this series averaged 9 years, and 77% of them were from 7 to 12 years of age. Only 10% of the dogs were under 7 years of age. This age

distribution is a little later than that for neoplasms in general in the dog, but it is clear that many of the mammary tumours have an onset at a much younger age, and some had been present for several months, or even for a few years, before removal.

While a large number of the affected bitches were spaniels, there is no clear indication of any special breed incidence.

In the bitch, there are generally either four or five glands in each mammary chain, the presence of the third, or abdominal, pair being inconstant. As in previous surveys, the posterior mammary glands were found to bear the most tumours. Of the 160 tumours in this series for which the site of origin was recorded, nearly 7 out of 10 affected one or other of the two posterior pairs of glands, and the third pair was least often affected. This may merely reflect the fact that the posterior glands are the largest.

Clinically, the benign tumours were largely recognized by the owners as forming unsightly "lumps" in the affected gland. Ulceration was not a sure sign of malignancy, nor on the other hand was a well-defined lesion invariably a benign one. Despite the statement in a well-known textbook (Lacroix and Hoskins, 1952, p. 504) that most mammary tumours in the dog are malignant, in our series proof of malignancy, that is the presence of metastases, was found only for 41 of the 424 dogs (just under 10%), although 187 of the tumours were histologically classifiable as malignant.

The current assessment of the lymph drainage of the mammary glands of the bitch is illustrated by Stalker and Schlotthauer (1936), and by Baum (1918). This earlier worker found that lymph vessels passed from the three caudal glands (of the five on one side) to the superficial inguinal lymph node, and from the three cranial glands (of five) to the axillary node. Baum found also (in this respect differing from Stalker and Schlotthauer) that these three cranial glands also drained through the abdominal and thoracic walls to the sternal node. Both reports indicate that there is no direct lymphatic connexion between the mammary glands of the two sides.

In our series, leaving aside 3 cases of sarcoma in, but not of, mammary glands, metastases from 38 tumours were distributed as follows: In under half the cases (17/38), the regional node in the strict sense was involved, and in a quarter (10/38) some other nodes were involved (in one case, for example, the superficial inguinal node was the only site of metastasis from a lesion in the anterior gland, and in another, the axillary node from a lesion in the posterior gland). In 2 out of every 3 cases (25/38), the lungs were affected, and in 1 out of 3 (13/38) there were metastases in more distant areas. Thus, from this series, the prognosis would seem to be poor as regards the operative treatment of malignant tumours once they have metastasized. This should not, however, deter the surgeon, for the histologically malignant tumours outnumbered the clinically malignant (metastasizing) tumours by 4 to 1, indicating that at least some operations may be successful.

From the pathological aspect, there are two striking features of mammary tumours in bitches: one, the common occurrence of mixed tumours containing mucoid, chondroid or bony tissue, and the other, the wide variety of malignant types that occur, including a high proportion of sarcomas and also of what may be mixed malignant tumours (Table I).

TABLE I.—CLASSIFICATION OF 436 MAMMARY TUMOURS FROM 424 BITCHES

Benign tumours	249	Malignant tumours	187
Simple tumours	19	Carcinoma	87 (21 with metastases)
Adenoma	8	Sarcoma	73 (13 „ „)
Fibroma	2	Complex malignant	27 (7 „ „)
Lipoma	9		
Mixed ("complex") tumours	230		

Our experience thus differs from that of Stalker and Schlotthauer (1936), who state that sarcoma of the mammary gland is rather rare.

There is some evidence to suggest that in the process of development of the benign mixed tumours the following stages occur: Firstly, there is a disproportionate proliferation of "interposed" cells, that is, of cells lying between the luminal epithelium of ducts or acini and the surrounding collagenous connective tissue. These "interposed" cells become embedded in mucoid matrix, which they may form, and which may be transformed into chondroid material. Cartilage also appears to form by metaplasia of intralobular connective tissue, and bone, and maybe bone-marrow, is formed either by endochondral ossification of the cartilage (which may have a twofold origin) or by intra-membranous ossification in the intralobular connective tissue.

Although the identification of these "interposed" cells is not always possible, there is sometimes an indication that they are actually myo-epithelial cells, as is shown by their position and their morphology, by their staining reactions, e.g. with Masson's erythron-saffron, and by their positive alkaline phosphatase activity.

Many of the malignant tumours of the bitch mammary gland have the structure of sarcomas—some are osteosarcomas, or chondrosarcomas (23/73 sarcomas), and others are mucoid spindle cell sarcomas (40/73). It seems that these sarcomas are the malignant counterpart of the various types (mucoid, chondroid or bony) of benign mixed tumours. In fact, the origin of some of these sarcomas from "interposed" cells can be seen in sections, and the possible myo-epithelial nature of the sarcoma cells is supported by the occasional demonstration of alkaline phosphatase activity. An interesting and baffling problem of interpretation is provided by malignant tumours which appear to be carcinosarcomas.

It would be premature to conclude that all these diverse types of mammary tumour are basically of one kind, but they are perhaps more closely related than appears at first sight.

In the *cat*, mammary neoplasms show many points of contrast with those of the bitch (Cotchin, 1957). They are chiefly malignant histologically (38 out of 44 tumours) and to a lesser extent clinically (11 of 38 showed metastases); they occur at a relatively somewhat later age (12 years, average); they are chiefly seen in the anterior mammary glands, and are mainly adenocarcinomas. Mixed mammary tumours must be uncommon in cats (although myo-epithelial cells are present in the glands).

Discussion

There arise two very interesting problems in regard to these mammary tumours.

(1) What is the explanation of the remarkable difference between the incidence of mammary neoplasms in the bitch and in the cow? At least three of the four factors (or groups of factors) concerned in the pathogenesis of mammary cancer in mice (Mühlbock, 1956) must be significant in this respect. Nothing is known of the mammary tumour agent in our domestic species, but, as regards genetic constitution, and hormonal and environmental factors, there are, of course, obvious differences in the number, structure, functional activity, and secretion product, between the mammary glands of the different species which must involve the possibility of differences in response of the glands to oncogenic stimuli.

A useful analogy may be drawn between the species differences of incidence of neoplasia, and of infectious diseases. The species differences in incidence of the latter are attributable to differences in the host response on the one hand, and in exposure to the organism concerned on the other.

We might thus expect to find species differences of response and exposure to apply just as well to the relationship of mammary gland to oncogenic stimuli, of which hormonal stimuli will be the most important.

Response.—It is known that the different species vary in their experimental response to the same kind of hormonal stimulus. Folley (1956), for example, shows how animals may be divided into three groups, according to the effect of œstrogen in evoking growth of ducts and alveoli.

Growth Effect of Œstrogen in Physiological Doses

Duct	Alveolus	Animal
+	+	Cow
+	0	Cat
0	0	Bitch

Although reports of the effect of œstrogens in the dog show varying results—*see* Houssay (1935); Trentin *et al.* (1952)—it seems reasonable to conclude that the response to oncogenic activities of hormones would also vary from species to species.

Exposure.—The different species vary in such factors as the occurrence of spontaneous ovulation and the development of pseudo-pregnancy, and their mammary glands are probably exposed normally to varying hormonal stimuli.

Spontaneous ovulation	Pseudo-pregnancy	Animal
+	0	Cow
+	+	Bitch
0	+ (after induced ovulation)	Cat

We might therefore postulate that the cow's udder does not develop neoplasms because it is either not responsive to certain oncogenic stimuli (perhaps a resistance bred in incidentally as a result of breeding for high milk yield?), or is not exposed to them (perhaps this is related to the most obvious function of the cow's udder, for it has been shown that in mice with the mammary tumour agent, lactation—the animals being allowed to suckle their young instead of having them removed at birth—retarded mammary cancer).

On the other hand, the bitch might normally be subjected to effective oncogenic stimuli. Trentin *et al.* (1952) have shown, using ovariectomized dogs, that while œstrogen alone does

not cause mammary development, œstrogens and progesterone may cause development comparable with that seen in pregnancy and that progesterone alone has a similar, but lesser and more variable, effect. In the bitch (Hoskins *et al.*, 1953, p. 280), it is generally considered that mammary neoplasms are more often seen in bitches that have not bred, or have bred only infrequently a long time previously, and have shown abnormalities of the sexual cycle. One important factor has been thought to be the occurrence of lactation after pseudo-pregnancy. Sheppard (1955) suggests that there is an increase of these "false" lactations, and it may be that they are a reflection of the way in which a normal house pet is kept. There is the possibility that the normal pseudo-pregnant stimulation of the bitch's mammary gland, not followed by normal lactation and involution, is a sufficient tumour-producing agent, and that pseudo-pregnancy itself might be looked upon as an abnormal physiological condition.

(2) In the bitch, what is the significance of the common occurrence of mucoid, chondroid and bony tissue in mixed tumours?

Some of the bone, at any rate, seems to form because of the presence of cartilage, and in turn some of the cartilage seems to form because of the presence of mucoid tissue, so that at least part of the problem turns on the significance of the mucoid change, and of the proliferation of "interposed" cells to which it is so often related.

A pertinent observation may be that of Elliott and Turner (1950), who state that it appears probable that a mucolytic enzyme or collagenase is elaborated by the cells of the growing mammary gland of the rat, and who relate this to the invasion of connective tissue by the growing glandular buds. Conversely, McFarlane and others (Turner, 1952) describe the process of involution in the cow's udder as one in which the connective tissue in the interacinar position increases. It would seem that these changes in the connective tissue (and in particular of the "basement membrane") must be related in some very intimate way to the growth and involution changes of the glandular epithelium and myo-epithelium, and it may be that the myo-epithelium plays a particularly important role, as suggested by its position. In the mixed mammary tumour, we may be seeing on a neoplastically magnified scale a distortion of normal growth and involutionary relationships between lumenal epithelium, myo-epithelium and connective tissue. Clearly we need to know more about these relationships, and their possible hormonal control.

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Professor Geoffrey Hadfield:

The Hormonal Status of the Breast Cancer Patient

The proliferation of normal mammary epithelium is totally dependent on an adequate supply, in optimal proportions, of ovarian œstrogen and progesterone together with a pituitary mammotrophic hormone. Total hypophysectomy inevitably leads to rapid atrophy of the mammary glands as well as the gonads and adrenal cortex but the atrophic mammæ grow vigorously if supplied with pituitary prolactin, progesterone and biologically active œstrogen. There is now ample evidence that about 50% of human breast cancers are also hormone-dependent, and that progressive cellular proliferation in these hormone-

dependent growths is conditioned by an adequate supply of the same hormones which are requisite for normal mammogenesis.

Lyons, Li and their associates (1955) have reported that, in hypophysectomized and gonadectomized virgin female and immature male rats, the atrophic mammæ which result from these operations show a vigorous growth response if the animal is given pituitary prolactin together with ovarian œstrone and progesterone, but that none of these hormones alone or in pairs can induce this growth response, and any combination of ovarian and pituitary hormones which did not contain prolactin was incapable of doing so. It is probable therefore that the proliferation of the cells of hormone-dependent human breast cancers depends not only on ovarian hormones but also on a pituitary mammotrophic factor which may be prolactin.

A complete endocrinological investigation of human breast cancer patients on a research basis is therefore likely to supply fundamental information regarding hormone dependence of this variety of cancer and may help in rationalizing treatment of this disease by endocrine ablation. Such investigations should include an estimation of urinary œstrogen and pregnanediol, together with a cytological study of the vaginal smear to estimate the degree of cornification of the vaginal mucosa.

In the laboratories of the Imperial Cancer Research Fund, urinary œstrogens are estimated in three fractions—œstrone, œstradiol-17β and œstriol—by the method introduced by Brown (1955) of the Medical Research Council's Endocrine Research Unit in the University of Edinburgh.

Pituitary function and particularly prolactin production is difficult to estimate. Pituitary gonadotrophin can be assayed by a standard method and should form an integral part of a full estimation of the hormonal status of the breast cancer patient. We have shown that pituitary prolactin is excreted in the urine of pre-menopausal women during the second or luteal phase of menstruation, and that if œstrone, progesterone and human female urine are administered to hypophysectomized weanling male mice their atrophic mammary glands show a vigorous growth response which is probably due to urinary prolactin of human origin in combination with the two ovarian hormones. Current research work on this problem may therefore help to divide breast cancer patients into two groups—those who are excreting prolactin in measurable quantities, and those who are not. It will then remain to correlate this classification with the effects on the breast tumour and its metastases of the operation of hypophysectomy. By these means it is hoped to devise a test to determine the selection of those patients who are likely to respond to hypophysectomy.

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Mr. W. P. Greening:

Adrenalectomy for Cancer of the Breast

Since cancer of the breast is by far the leading cause of death among women in the mid-period of life, the palliative treatment of advanced recurrent and metastatic disease is a major problem in clinical management.

The treatment of metastatic cancer by the administration of hormones or ablative surgery depends on the fact that certain breast tumours are apparently hormone-dependent.

Adrenalectomy for patients with widely disseminated cancer was first carried out by Huggins in 1948 and is now an accepted surgical treatment for certain cases of malignant disease (Huggins, 1952). Apart from an increasing knowledge due to experience of the clinical aspect of the problem, there have been few advances either on the pathological or biochemical side.

From an historical point of view, Loeb in 1919 published a paper on the origin of breast tumours in mice. He had found that castration between three to six months almost entirely prevented cancer of the breast, whereas in mice castrated at seven to ten months, no immunity was obtained.

Woolley *et al.* (1939) ovariectomized 83 mice at birth, nevertheless 26% developed mammary tumours at an average age of 522 days. A careful check was made at post-mortem for any residual ovarian tissue, but none was found. At six months the uterus was atrophic, but later it became enlarged and hypertrophied, there was also in the breasts extensive duct development with the presence of end buds. It was noted that the adrenals in all cases were enlarged and had yellow nodules in them. The hypertrophy was in the cortex and it was these lesions which were secreting steroids in sufficient quantities to cause activity in the uterus and breasts and to induce tumours in the mammary glands.

Œstrogen-induced tumours in the mammary gland have been described by Cramer and Horning, and Burns and Horning have shown that they may also occur in the uterus and kidney.

The supply of œstrogen must be continuous, and it is interesting that the œstrogen-induced tumours may be limited to one organ only, and even to certain species of animal. Ovariectomy does not eliminate the excretion of œstrogen in the urine and, in time, a considerable rise in its production can be detected. This raised excretion is accompanied by hypertrophy of the cortex of the adrenal glands and they must therefore be regarded as a source of production of œstrogenic hormones.

Beatson is generally accepted as the first to suggest the possibility of hormone responsiveness in tumours in man. He was interested in lactation and noted that the cellular proliferation and desquamation were associated with a cessation of ovarian activity. He, therefore, carried out ovariectomy in cases of breast cancer, but reinforced his operation by giving thyroid. In the mistaken belief that he was advising this treatment for early breast cancer, his work was the object of much criticism.

In 1942, Adair and Farrow reported a remarkable remission in cancer of the male breast following orchidectomy, and this work was confirmed by Treves (1949), who also collected 116 female patients who had prophylactic castration and compared them with 2,893 non-castrated cases. In the non-castrated the five-year survival was 54·4%. In the castrated the five-year survival was 63%.

In an attempt to "neutralize" œstrogen, testosterone was first used by Loeser in 1938, and the remarkable remissions produced by this hormone are well known. Galton (1950) found, in a series of 70 cases, that over 40% were improved. Surprisingly, synthetic œstrogen used by Haddow and his co-workers in 1944 also produced a remarkable remission, for periods of anything from one to nine months. Although this would appear difficult to explain, it is possible that the results achieved are due to inhibition of the adrenocorticotrophic hormones of the hypophysis. The isolation and production of cortisone enabled Huggins, for the first time, to remove the œstrogen-producing adrenals and ovaries and at the same time to maintain the patient in completely normal health. The complete elimination of œstrogen production, however, only caused a remission in 40% of adrenalectomized and ovariectomized patients and this remission, although often apparently complete, was not maintained on an average for more than two years, but occasionally for as long a period as five years. It is assumed, therefore, that one of three things must be happening to cause a further growth of the disease. (1) There is still œstrogen production from ectopic ovarian or adrenal tissue. (2) A hypophyseal mammotrophic hormone may reactivate the cells; or (3) the tumour may no longer be hormone-dependent. The complete removal of the hypophysis eliminating, therefore, mammotrophic hormone production and steroid hormones from the adrenals and ovaries, should, on this reasoning, produce a much higher percentage of remissions, with a corresponding increase in their duration. Surprisingly, the figures are only 10% better.

The reasons, therefore, for removing the adrenal glands and ovaries in mammary cancer are:

(1) Ovariectomy may cause remissions of breast cancer in the human and will delay its onset in animals.

(2) The adrenals can also produce sufficient quantities of steroids to maintain a hormone-dependent neoplasm.

(3) Increased œstrogen excretion in ovariectomized animals is associated with adrenocortical hyperplasia and the production of mammary tumours.

Because there has been no specific test for hormone responsiveness and therefore no reliable method of predicting results, there has been a tendency to reserve the operation for *all* cases where no other treatment is possible. There are a few indications which help, but the success or failure of the operation is so unpredictable that one has hesitated to advise against adrenalectomy in case the last chance of remission is denied the patient. The condition, while it must not be hopelessly advanced, should not be able to be kept under control by simpler methods. Localized bony deposits and isolated pleural effusions are best treated by some form of radiotherapy, and here it is important to remember the variable course of the disease. Metastatic breast cancer may remain static or fail to progress for a considerable time and adrenalectomy should be reserved for those cases that are definitely progressing.

We find that the majority of remissions occur between the ages of 45 and 50. High values of œstrogen excretion in the urine at all times, and particularly after ovariectomy or the menopause, indicate significant adrenocortical activity and therefore the possibility that adrenalectomy will cause a remission.

The histology of the tumour is of little help in most cases. It varies in different parts of the primary and the metastatic deposits and quite commonly one tumour may show different structural variants.

Two methods have been described by Emerson and Jessiman (1956) by which hormone dependency may be evaluated; the sex-hormone stimulation test, in which results are assessed by observation of the increase in urinary calcium excretion and subjective symptoms after the administration of stilbœstrol; and (2) the cortisone inhibition test, in which the result is

judged by the decrease in urinary calcium excretion and improvement in subjective symptoms.

The effects of adrenalectomy are seen as either subjective or objective improvement. Subjective improvement is often dramatic and occurs in at least 60% of cases. It consists of relief of pain from bony deposits, improved appetite, gain in weight and an increased feeling of well-being. This subjective remission is of little importance unless accompanied by objective changes. It is due to the administration of cortisone which not only relieves pain and causes euphoria, but also, in those cases with hypercalcæmia, immediately lowers the calcium excretion in the urine. The symptoms of hypercalcæmia are vomiting, thirst, drowsiness and pain.

Laboratory findings show that by and large there has been little alteration from normal. Apart from those patients with bone metastases, we find no change either before or after operation in the blood calcium or phosphates values. When metastases in bone are present, the blood calcium and the urine excretion values are raised in about one-quarter of the cases.

In a high proportion, nearly half, the serum alkaline phosphatase is elevated. This indicates osteoblastic activity or liver disease. In women with osteolytic secondaries, therefore, elevation of the serum alkaline phosphatase after therapy indicates increased osteoblastic activity and therefore healing of metastases.

Ketosteroid estimations diminish markedly in all patients after adrenalectomy. There is no significant increase in their value before operation.

Œstrogen excretion is temporarily abolished by adrenalectomy and ovariectomy and reference has already been made to the variable levels in breast cancer cases.

Gonadotrophin assays are being carried out but it is too early to say whether we are going to find any significant changes.

From the numerous reports of the effect of bilateral adrenalectomy for advanced cancer of the breast, there appears to be a definite dissociation between subjective and objective improvement. Relief of pain and increased feeling of well-being occur in approximately 60% of the patients. Objective remissions occur in only 30%. The average duration of objective remissions, in which there has been complete, or almost complete, disappearance of metastases, is approximately two years. In all cases when the disease recurs, there is a preponderance of new lesions rather than reactivation of previously healed ones. Both androgens and œstrogens have been used at this stage but have failed to alter the course of the disease apart from accelerating it.

If the recurrences are chiefly skeletal and osteolytic, increased cortisone may help to control the symptoms. It is too early yet to draw any definite conclusions as to the effect of hypophysectomy in adrenalectomized patients, but it would appear that a further remission may be obtained, and this has certainly been our experience in a limited number of cases. In patients who have been adrenalectomized and have thereby obtained objective remission with apparent complete regression of the disease, hypophysectomy is successful in only 40%—a figure similar to that obtained by adrenalectomy in completely unselected cases.

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Dr. I. Lewin:

Xanthine Oxidase Activity in Normal and Abnormal Growth

A. Levels of Xanthine Oxidase Activity during Normal Growth

Xanthine oxidase activity was measured in mammæ in a total of 115 C+ mice during the virgin state, pregnancy, lactation and involution. Since this organ undergoes profound changes in size, structure and function during the reproductive cycle, it was necessary to search for an expression of enzyme activity which would permit biological interpretation. Of the many indices, such as wet weight of tissue, defatted dry weight, total nitrogen, DNA and cell count, it would seem that the expression of enzyme activity as a function of the variable cellularity would best reflect the changes in a growing tissue. Also, in order to unify the presentation of the data, the observed absolute values are expressed as a percentage of the baseline value, that is, the average value obtained in breasts from up to 50 virgin mice.

I. *Changes in weight.*—In each case, the five pairs of breast pads were stripped off the underside of the skin and weighed. The tissue was then minced with fine scissors and an aliquot was removed for the determination of water, fat and defatted dry weight compositions.

FIG. 2.—Cell number, DNAP, and DNAP per nucleus in mammæ of C+ mice during the reproductive cycle.

FIG. 3.—Changes of weight and composition of mammæ from C+ mice during the reproductive cycle.

Another sample was taken from a pyrophosphate homogenate for total nitrogen. The results are shown in Fig. 1.

From an average value of about 400 mg. of total mammary tissue in a virgin mouse, the mammæ increase in weight to about 1,800 mg. around the middle of the lactation phase. During the first 16 days of pregnancy the increase in weight seems slower than during the last 3 days of pregnancy. It has not been estimated how much of the further weight increase beyond the moment of parturition is due to milk retained in the ducts and alveoli of the mammæ although the litter is allowed to nurse until the sacrifice of the mouse. According to Folley and Greenbaum (1947), the milk content may be between 40 and 50% of the weight of the mammæ in rats. A decrease in breast weight occurs towards the later part of lactation and is accelerated after weaning.

The wet weight can be thought of as being the sum of the amount of water, fat and defatted dry matter. In the latter the proteins constitute the major proportion. During the virgin state the mammæ are composed of 65·7% fat, 26·5% water and 7·7% defatted dry matter. At the height of development during lactation these values become 12·8% fat, 68·7% water and 18·2% defatted dry matter. After weaning there is prompt return towards the baseline. The amount of total nitrogen per mg. of fresh tissue also increases during pregnancy and continues to do so after parturition, which may be a reflection of milk production and retention. In regard to water, fat and nitrogen content one can distinguish a slow phase of change (up to about the 16th day of pregnancy) and an accelerated phase during the last 3 days of pregnancy.

II. *Changes in cellularity.*—The change in weight of the total mass of mammary tissue is seen to be the resultant of changes in fat, water and protein content. A better measure of the change in tissue mass is an estimate of cell numbers. However, the expression of cell number per unit of weight would also be inadequate since it would be affected by the fluctuations in fat and water content as well as by the amount of milk retained in the mammæ during the later part of pregnancy and lactation. To obviate these fortuitous variations in cell concentration, the total number of nuclei were calculated for all breast pads in a mouse. The nuclei in a sample from a sucrose-$CaCl_2$ homogenate were counted in a hæmacytometer and the number of nuclei per mg. of wet tissue were multiplied by the total weight of the mammæ in a mouse.

In the majority of samples, the sucrose-$CaCl_2$ homogenate was also used for DNA determinations. The homogenate was centrifuged at 20,000 × *g* for 30 minutes at 0° C. the solidified fat layer was skimmed off, the sediment was resuspended and an aliquot was treated with 10% TCA in the cold for one hour. The precipitate was washed with 5% TCA and then heated with two portions of 5% TCA at 90° C. for fifteen minutes each. The two extractions were pooled and boiled for fifteen minutes after mixing with the diphenylamine reagent. The colour was read at 600 mμ in a SP 500 Unicam Spectrophotometer and compared with a DNA standard.

Fig. 2 shows the great increase in total cell numbers from about 30×10^6 in a virgin breast to a maximum of 450×10^6 at around the 4th to 6th day of lactation. The increase in cells is greater (about fifteen-fold) than the increase in weight (about four-fold). This simply reflects the fact that almost all of the rather large adipose cells are replaced by smaller ductile and acinar cells of the mammary gland proper. A decrease in total cell number starts already around the 6th day of lactation. It is suggested that the reason for this early decline is the involution of some of the breast pads, usually the 1st and 2nd thoracic mammæ, which are not used by the litter.

The amount of DNAP (desoxyribose nucleic acid phosphorus) in the total breast parallels the changes in cell number, so that the amount of DNAP per nucleus remains fairly constant during pregnancy and lactation. The average value in this series of forty determinations on mammary tissue is $1{\cdot}196 \times 10^{-12}$ gram of DNAP per nucleus. For mouse liver Laird (1954) and Tsuboi *et al.* (1954) have reported values of $1{\cdot}23 \times 10^{-12}$ and $1{\cdot}36 \times 10^{-12}$ grams of DNAP per nucleus, respectively. These observations would indicate that the determination of the number of nuclei in a homogenate is a valid measure of cellularity.

The series here reported supports the observations that the mammæ continue to grow throughout pregnancy and part of lactation. Greenbaum (personal communication) in studying mammæ of rats has found that on the last day of pregnancy the DNA per gram of wet tissue has increased ten-fold and on the 3rd day of lactation sixteen-fold when compared to the virgin breast which means that the amount of DNA approximately doubles during the first few days of lactation. Histological evidence that the growth of the mammæ continues into lactation has been supplied by Cole (1933) who reported that mitosis of breast cells can be observed until the 7th day of lactation, although in diminishing numbers. However, Turner has stated that in mice the hyperplasia of the mammary gland parenchyma is complete by the 12th day of pregnancy (Turner and Gomez, 1933) and that in rats the amount of DNA content in the inguinal breast pads has reached a maximum at about the

Changes of weight and composition of mammæ from C+ mice during the reproductive cycle.

FIG. 2.—Cell number, DNAP, and DNAP per nucleus in mammæ of C+ mice during the reproductive cycle.

10th day of pregnancy after which it remains level until the time of weaning (Kirkham and Turner, 1953). No explanation can be offered for these differences, except that they may be due to differences in strain and species.

III. *Changes in xanthine oxidase activity of mammary tissue.*—The xanthine oxidase activity of the homogenate was determined by measuring the rate of uric acid formation. The rate per mg. of wet tissue was related to nuclear count. defatted dry matter and total nitrogen per mg. of wet tissue; thus eliminating the variations introduced by the changes in water and fat content of the mammæ during pregnancy, lactation and involution.

Fig. 3 shows the results. From an average baseline level in the virgin breast of $4{\cdot}2 \times 10^{-5}$

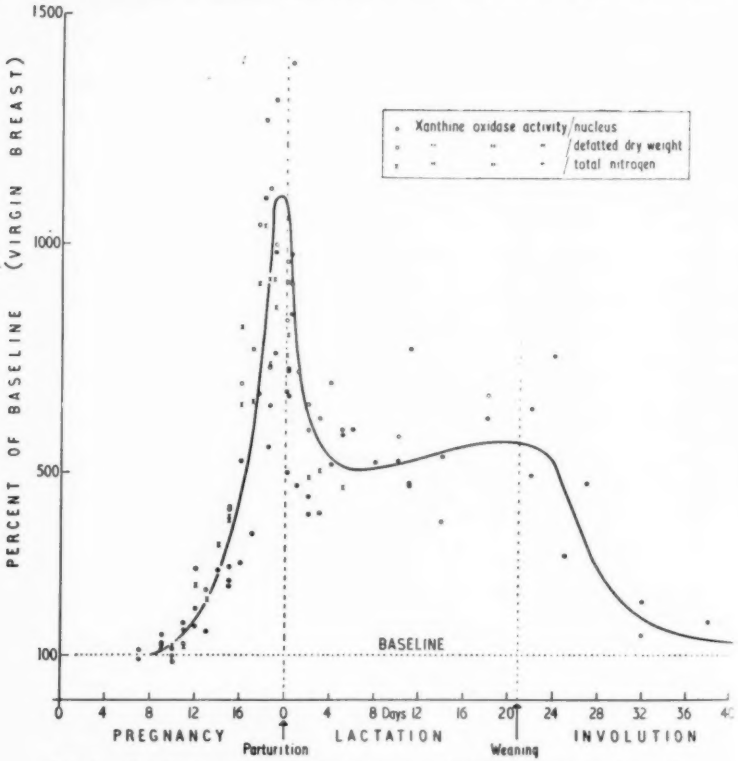


FIG. 3.—Xanthine oxidase activity in mammæ during the reproductive cycle.

micromoles of xanthine oxidized per minute per 10^5 nuclei the xanthine oxidase activity rises from about the 10th day of pregnancy onwards to a maximum value of $46{\cdot}2 \times 10^{-5}$ at a time shortly before parturition; this activity drops precipitously to about half this value for the duration of lactation. A decrease in xanthine oxidase activity becomes noticeable a few days after weaning, but does not seem to reach the baseline level even 17 days after weaning. All three indices (enzyme activity per cell per defatted dry matter or per total nitrogen) yield practically the same curves and indicate the overall net increase in this enzyme.

The peak in enzyme activity just before parturition is surprising and needs further comment.

IV. *Xanthine oxidase activity in milk.*—One of the earliest and richest sources of this enzyme is cow's milk. It was therefore essential in this investigation to evaluate the effect of mouse milk on the determination of xanthine oxidase in mammæ of mice during late pregnancy and lactation. It was noted that in some mice the mammæ were completely filled with milk, appearing engorged and white, whilst in other animals of the same dam in pregnancy or lactation the mammæ were entirely pink and presumably containing no so much milk. However, there was no consistent or significant difference in the xanthine oxidase activity either per unit of weight or per cell between the homogenates from presumably "milk-rich" and "milk-poor" mammæ. In order to follow up this observation a mouse

the 8th day of lactation was separated from its litter for twelve hours and then the breast pads of the left side were freed of milk as much as possible by "milking" and compared with the milk-engorged breast pads of the right side. The results (Table I) show that there is no

TABLE I.—COMPARISON OF XANTHINE OXIDASE ACTIVITY IN MAMMÆ CONTAINING DIFFERENT AMOUNTS OF MILK

Tissue	Appearance	Weight (mg.)	Amount of milk removed (ml.)	Nuclei/mg. of wet tissue ($\times 10^3$)	Micromoles ($\times 10^{-5}$) of xanthine oxidized/minute per mg. wet weight	Micromoles ($\times 10^{-5}$) of xanthine oxidized/minute per 10^5 nuclei
Breast pads of the right side (control)	White; engorged with milk	1,210	0·0	151	32·3	21·4
Breast pads of the left side ("milked")	Entirely pink	800	0·341	184	39·2	21·3

difference in xanthine oxidase activity per nucleus while the activity per mg. of wet tissue is slightly higher in the homogenate of the "milked" mammæ. Had the milk contributed to the xanthine oxidase activity one would have expected the homogenate of the right breast pads (control) to have a greater activity per nucleus and to have the same activity per mg. when compared to the left mammæ.

At this point it should be pointed out that the tissue homogenate is centrifuged at 20,000 × *g* for 30 minutes at 0° C. and the clear supernatant is incubated for one hour in a 37° C. incubator prior to the assay. The effect of these preparatory steps on milk xanthine oxidase was tested on 3 milk samples obtained from mice during lactation. "Milking" was accomplished as follows: the mouse was separated from its litter for twelve hours in order to allow the milk to accumulate, the hair was clipped around the nipples, under ether anæsthesia 1 ml. of Pitocin containing one international oxytocic unit was injected intraperitoneally and the tips of the nipples were cut off three minutes later. After starting the flow of milk by suction with a water pump, the milk flowed freely and could be collected by means of a pipette. Up to 1·5 ml. of milk could be obtained in this way. In each case, high speed centrifugation reduced the activity of the milk by 75–100% of the original value, while incubation hardly altered the enzyme activity (Table II). This is in contrast to the

TABLE II.—EFFECT OF INCUBATION AND CENTRIFUGATION UPON THE XANTHINE OXIDASE ACTIVITY OF BREAST TISSUE AND MOUSE MILK

Material	Centrifugation	Micromoles ($\times 10^{-5}$) of xanthine oxidized/min./mg. wet weight: No incubation	Incubation
Mammary tissue	600 × *g*; 10 min.	21·3	49·8
	20,000 × *g*; 30 min.	—	47·7
Milk	None	17·5	18·6
	20,000 × *g*; 30 min.	—	0·0

tissue homogenate where enzyme activity is increased by incubation but not materially altered by centrifugation.

This difference in response to the centrifugation neatly eliminated the so-called "milk error" usually present when experimenting with mammary tissue during lactation. However, since it could still be possible that the milk in the presence of tissue acts differently from milk alone, the experiment listed in Table III was performed. Breast tissue and mouse milk were

TABLE III.—XANTHINE OXIDASE ACTIVITY IN MIXTURES OF MAMMARY TISSUE AND MOUSE MILK AFTER CENTRIFUGATION AND INCUBATION

Preparation No.	Mammary tissue (g.)	Mouse Milk (g.)	Tissue concentration (%)	Micromoles ($\times 10^{-5}$) of xanthine oxidized/min./mg. wet weight	Enzyme activity as percentage of Preparation No. 1
1	0·3781	0·0	100·0	47·7	100·0
2	0·1441	0·0658	68·8	34·2	71·8
3	0·1009	0·1044	53·5	24·6	51·5
4	0·0550	0·1494	26·9	9·1	19·1
5	0·0	0·3712	0·0	0·0	0·0

mixed in varying ratios and a 1+9 homogenate prepared in pyrophosphate buffer (0·1 M, pH 8). The assays were performed in the usual manner after high-speed centrifugation and incubation of the material. In comparing the last column with the tissue concentrations it is evident that the entire xanthine oxidase activity in the tissue-milk mixture is accountable for in terms of the tissue enzyme alone.

The fact that the xanthine oxidase activity of mouse milk is sedimentable corroborates the finding of Morton (1954) that in cow's milk this enzyme is attached to lipoprotein particles which can be sedimented by centrifugation at 14,000 × *g*. Our own experiments have shown that in homogenates of mouse breast and liver and of rat liver almost all of the xanthine oxidase is recoverable from the supernatant fraction after high speed centrifugation (20,000 × *g*) and that no activity can be found in the particulate matter. Meikleham *et al.* (1951), Villela *et al.* (1955) and Morell (1955) have already reported that the xanthine oxidase from rat liver and the xanthine dehydrogenase from chicken liver are in the supernatant fraction after high speed centrifugation. It would be of interest to establish the point during milk formation and secretion at which the soluble tissue enzyme becomes a sedimentable component of milk.

Although it could be shown that the milk xanthine oxidase does not affect the determination of this enzyme in mammæ during lactation, the situation might be different in regard to the milk accumulating in the breasts prior to lactation. In order to test this possibility a mouse was "milked" at the beginning of parturition. This first milk, or colostrum, however, was similar to the milk obtained at the height of lactation: centrifugation caused a virtual disappearance of the xanthine oxidase activity of the colostrum. One possible explanation, therefore, for the peak in xanthine oxidase activity preceding parturition is that it represents an accumulation of intracellular enzyme proper ready to be incorporated into milk enzyme. The disappearance of this peak during lactation would thus reflect the high rate of milk production and secretion.

V. *Xanthine oxidase activity in liver.*—Pregnancy and lactation are associated with profound hormonal and metabolic changes. It was therefore of interest to compare the liver with the mammary tissue in regard to xanthine oxidase since this enzyme in the rat liver is very sensitive to fluctuations in protein metabolism (Westerfeld and Richert, 1950). The average level of xanthine oxidase activity per nucleus did not vary significantly throughout the reproductive cycle and when compared to the livers from virgin mice. It was seen that, while the enzyme activity per cell is about 60% greater in the liver than in the breast during the virgin state, the enzyme activity becomes three to five times greater in the breast than in the liver during late pregnancy and lactation. There is a small but statistically significant increase in the total number of liver cells during pregnancy, lactation and the observed period after weaning.

B. Levels of Xanthine Oxidase Activity during Abnormal Growth

The increase in the number of mammary cells leading to a functioning gland is associated with an increase in xanthine oxidase activity per cell. Two questions arise from this observation: (1) What are the levels of xanthine oxidase activity in tumours as compared to the tissue of origin? (2) What happens to the enzyme during the growth of the tumour?

The data reported in the following section have been obtained in an attempt to answer these questions.

I. *Xanthine oxidase activity in spontaneous breast tumour.*—The design of this experiment entailed a comparison of xanthine oxidase activity in mammary tumour and in mammary tissue from cancer-susceptible and cancer-resistant mice of the same strain. Inbred mice of the C— strain constituted the cancer-resistant group. These mice do not possess the milk agent (Bittner factor) and develop mammary tumours only rarely even after many pregnancies. Cancer-susceptibility was imparted to the C— strain by foster-nursing on C_3H mice, thus incorporating the milk agent. Mice of this highly-inbred sub-line, here called C+, rarely develop mammary tumour if they remain virgins, but will have a 100% tumour incidence at an average age of 7 months if force-bred. The material for the tumour series was obtained from these C+ mice.

The results are summarized in Fig. 4. The differences in the average levels of enzyme activity per cell are highly significant, $P = < 0{\cdot}001$ when comparing groups A and C to B. Relative to the enzyme activity of breasts from C— mice, the activity in breasts from C+ mice is 57·7% and in tumours 24·9%. It should be stressed that the breasts in group B derive from animals that had no tumour and would as a rule not develop such. The difference in xanthine oxidase activity in the mammæ of C— and C+ mice can therefore be related to the absence or presence of the milk agent in the cytoplasm and not to the genetic constitution or the actual presence of a tumour. The enzyme activity in the normal parts of the breasts from mated C+ mice with tumours is similar to that in breasts of C+ virgin mice.

In contrast to the enzyme in the breast, the xanthine oxidase activity in livers of C— and C+ mice does not differ materially. This is in line with the observation that the liver contains relatively small amounts of milk agent. However, Figge and Strong (1941) found a marked difference in xanthine oxidase activity of livers from mice with a high and mice with a low incidence of breast tumour, the C_3H and JK strains respectively. But the desi of

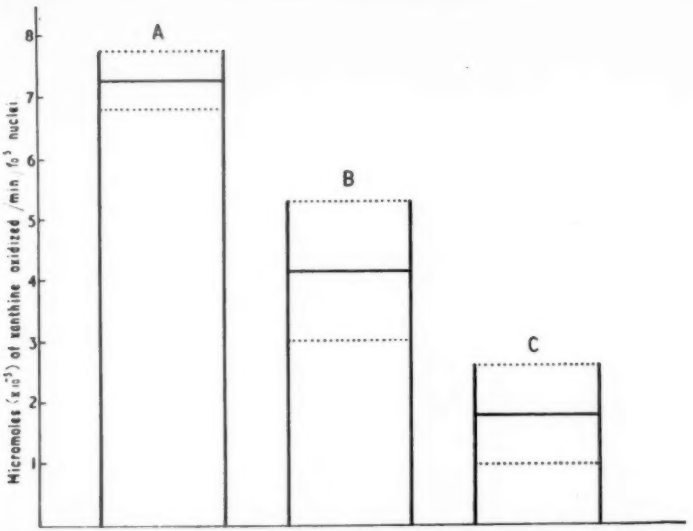


FIG. 4.—Xanthine oxidase activity during carcinogenesis in mouse breast. A, Virgin breast from low tumour strain (C−) without milk factor; 25 animals. B, Virgin breast from high tumour strain (C+) with milk factor; 50 animals free of tumours. C, Spontaneous mammary tumour from mated (C+) mice; 24 animals. (Dotted line indicates ± S.D.)

their experiment makes it difficult to decide whether the difference in enzyme activity reflects a difference in cancer-susceptibility or in genetic constitution.

The tumours used ranged from 0·3 grams to 7·0 grams and could be divided into solid, firm grey and soft, hæmorrhagic purplish tumours. Histologically, they were all adenocarcinomas but showed varying degrees of dedifferentiation. For purposes of the assay necrotic material was avoided. There was no significant difference in the enzyme activity of the different kinds of tumours. Each average mammary cancer cell possesses one-fourth the xanthine oxidase activity contained in the average normal mammary cell and one-half the activity present in a precancerous breast cell (a cell infected with the milk agent).

Since there is no statistically significant difference in the cellularity of breasts from virgin mice of the C+ and C− strain, it is concluded that the xanthine oxidase activity is lowered in the precancerous state, whether expressed as enzyme concentration (activity per mg.) or as content (activity per cell).

II. *Xanthine oxidase activity in liver tumours.*—These experiments were performed in collaboration with Dr. E. Reid and the methods of producing liver tumours in rats by means of azo-dye are described by him (Reid and O'Neal, 1957). The data are presented in Fig. 5. Since nuclear counts were not performed in this series the enzyme activity is expressed per mg. of wet tissue. Because of the small number of observations a statistical analysis of the difference of the means was not performed, but the graph reveals no overlap of the individual values comprising each group.

There is good agreement between the observations here reported and those previously published involving different techniques of assay, different strains and different tissues. Westerfeld *et al.* (1950) have studied the xanthine oxidase activity in rat livers during carcinogenesis by measuring the consumption of oxygen and have reported a 50% decrease in enzyme activity per dry weight in tumour-free livers from rats receiving *p*-dimethylaminoazo-benzene for four weeks. Greenstein (1947) reported on the xanthine dehydrogenase activity, measured by reduction of methylene blue, in transplanted mouse and rat hepatomas as compared to the respective tissues of origin: of six different hepatomas, five had an enzyme activity per mg. nitrogen of $\frac{1}{2}$ to $\frac{1}{4}$ the level in normal liver.

Deficiency states in tissues from tumour-susceptible animals, in precancerous tissues or in fully developed tumours have been demonstrated repeatedly. Bittner found that the esterase level is lower in livers from cancer-susceptible than in livers from cancer-resistant mice. Weiler (1956) was able to show by an ingenious histo-serological technique the loss of a liver-specific antigen during azo-dye carcinogenesis. However, β-glucuronidase has a higher

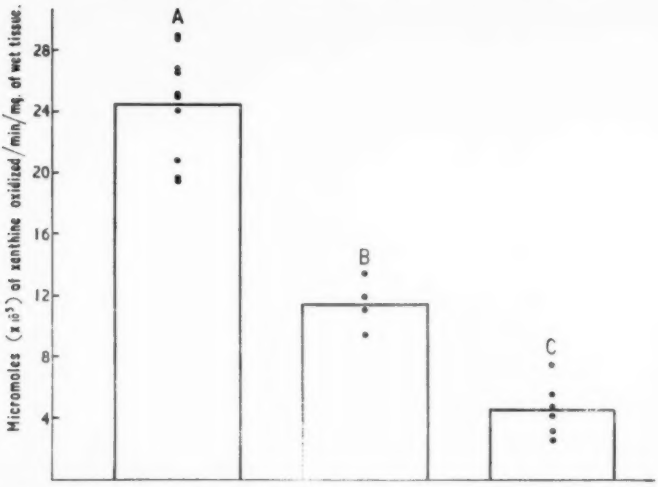


FIG. 5.—Xanthine oxidase activity during carcinogenesis in rat liver. A, Normal liver from rats on normal diet. B, Tumour-free liver from rats fed azo-dye for a short period. C, Liver tumour in rats fed azo-dye. (Dots indicate individual values.)

level in tumour than in the mother tissue; but here too the precancerous tissue has an intermediate level of enzyme activity. It would seem that changes during carcinogenesis are in the direction that leads to the ultimate state existing in the tumour.

III. *Growth and xanthine oxidase.*—The data of the enzyme activity in breast pads from pregnant mice and in spontaneous mammary tumours was expressed as a function of growth, that is, enzyme activity per cell was plotted against the fresh weight of the total tumour or total breast pads. While growth of the mammæ leading to the formation of a normally functioning tissue is associated with an ever-increasing level of enzyme activity per cell, no such gain in enzyme activity is present in the cells of growing mammary tumours.

Growth in the case of the tumour means no more than cell multiplication resulting in an increased tissue mass, whereas in the mammæ there is also a change in function besides the increase in cellularity. Since growth can proceed without an increase in xanthine oxidase activity per cell, as in the mammary tumour, or even in the virtual absence of this enzyme, as in embryonic tissue, the increase of this enzyme per cell in the mammæ is best related to their gain in specialized function preparatory to the secretion of a product so rich in this enzyme. Hence, if one assumes, as one should, I believe, that the cell of origin is the same for the lactating mammæ and the mammary cancer, the failure of the tumour to increase its level of enzyme activity is just another expression of the loss of specialized function of this dedifferentiated tissue.

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Section of Orthopædics

President—E. STANLEY EVANS, C.B.E., F.R.C.S.

[*March* 23, 1957]

MEETING AT KING'S COLLEGE HOSPITAL, LONDON

117 CASES were shown demonstrating the following conditions:

High femoral osteotomy; Double hip operations; Median and ulnar palsy; Diffuse hæmangioma of leg; Unusual rheumatoid arthritis; Dysfunction of the first metatarso-phalangeal joint; Acute osteomyelitis; Lesions of the feet in diabetes; Idiopathic pes cavus; Leg lengthening; Congenital phocomelia; Late results of slipped upper femoral epiphysis; Fractures of the tibia; Monostotic fibrous dysplasia; Caffey's disease; Knock-knee following osteomyelitis of lower end of femur; Congenital bowing of leg; Arthroplasty of elbow; Pseudarthrosis of elbow; Acroparæsthesia treated by means of a splint; Talipes equino-cavus—metatarsal osteotomy; "Genuine" congenital dislocation of the hip.

The use and abuse of the "Resettlement Case Conference" was discussed on four particularly difficult medico-social problems with Dr. F. S. Cooksey.

After Demonstrations of pathological specimens (Professor H. A. Magnus) and Occupational Therapy appliances for disabled persons, the following papers were read:

Conservative Treatment of Carpal Tunnel Syndrome.—Dr. R. HIERONS.

Tendon Lesions in the Rheumatoid Hand.—Dr. D. A. BREWERTON.

Presentation of Group of Fractures of the Tibia.—Mr. R. H. FREEMAN.

Provision of Skin Cover.—Mr. F. T. MOORE.

[*April* 2, 1957]

Changing Patterns in Skeletal and Articular Tuberculosis

PRESIDENT'S ADDRESS

By E. STANLEY EVANS, C.B.E., F.R.C.S.

IN this brief survey of orthopædic tuberculosis I shall begin by referring to the changing patterns of skeletal and articular tuberculosis which are now chiefly of historical interest.

Motherby's New Medical Dictionary published in 1775 contains the classification of spina ventosa or caries of bone by Percivall Pott as hydrops articuli, fungous articuli and the enlargement of bone. Treatment was directed towards promoting the absorption of fluid by blisters, by inunction of mercury and antimony and sometimes with advantage following the electric shock. "The third type—enlargement of bone, is sometimes relieved by perforations made through the diseased parts to the marrow, but most frequently amputation is necessary. The friability of carious bones is much augmented by the acrimony of their humours and chiefly by their corrupted medullary oil. Chronic abscesses in the back and loins are generally of the strumous kind, the matter is usually deep seated and the bones are injured by it before a fluctuation can be discovered." I shall return to the problem of the abscess arising from bone and subsequently causing injury or spread of infection into healthy bone. Sea water was popular in the treatment of glandular swellings. It was known that scrofula (from Scrofa—a sow, because the disease occurs in swine) or the King's Evil which kings from Edward the Confessor onwards pretended to cure by the touch, could affect almost every part of the body and that the lymphatic vessels and glands were the immediate seat of the trouble. The fixed immovable white swellings of joints are compared with the strumous swellings of the neck.

Percivall Pott, one of the great surgeons of the oldest London hospital (still on its

original site) wrote a treatise in 1779 entitled "Remarks on that kind of palsy which is frequently found to accompany a curvature of the spine" and a specimen prepared by him to show the diseased vertebræ in such a case was placed in the museum of St. Bartholomew's Hospital. There was no better description of Pott's paraplegia until the outstanding papers in our time by Seddon and Butler and the recent excellent monograph by Seddon, Griffiths and Roaf.

The approach to the problems posed by the strumous disorders in the early part of the nineteenth century can perhaps best be gleaned from a perusal of the excellent lectures delivered by John Abernethy in the medical school at St. Bartholomew's Hospital which he founded. He paid great attention to his lectures and never forgot that a lecture is to be valued not only by what the lecturer puts into it, but by what the hearer can carry away from it. The *Lancet* of 1824 embodies his course of surgical lectures (in which he frequently refers to his debt to the immortal John Hunter) which he delivered to a very numerous and highly respectable class. Abernethy embellished his lectures with graphic descriptions of the patients he attended and perhaps I may be permitted to quote one case. He records: "I was requested to see a young lady, a long way in the country, even in Wales and in a very remote part of the principality too, who had a lumbar abscess. I went and I found that there was a large collection of matter in the fore-part of the thigh, that the spine was much distorted, the countenance flushed, and the constitution altogether in a very irritable state."

As she was then amongst the mountains of Wales Abernethy advised that nothing need be done, but that she be kept in a state of quietude, that some counter-irritation should be made and that the state of the digestive organs be attended to. The young lady continued to get stronger day by day and the disease gradually subsided under this excellent general and local conservative treatment. After about a year, and without consulting Abernethy, a person was sent down from London to fit a machine and the father wrote in eulogistic terms of the spinal stays, which by screwing it up could raise his daughter in height two inches. Abernethy replied: "In the name of common sense, Sir, only consider what a state the vertebral column must be in which will admit of such elongation by any artificial means." He advised that they should lay the machine aside and return to the former plan. Some six years later the young lady was cured of her phthisical complaint in Bristol after taking a course of muriate of lime and Abernethy was aggrieved to find the excellent state of her spine was ultimately attributed to the muriate of lime and not to the constitutional treatment he had advocated.

In dealing with a lumbar abscess connected with a diseased state of the vertebral column he insisted that the patient should be required to be in bed and not allow the diseased parts to move about, and added that the abscesses frequently subsided and diminished in size if attention is paid to the state of the general health. If necessary he lanced the abscess in order "that it never might be opened", and he tried to prevent foul air entering the abscess after puncture by pressure on the abscess and by applying lint and adhesive plaster. He knew nothing of the bacteriology of secondary infection, but his experience had taught him that the abscess should not be allowed to drain openly. After puncturing the abscess two or three times the patient fancies he is almost well, but Abernethy is mindful of the dangers and advises continued rest in bed and "if he could be sent into the country it would do him much good".

He describes how on one occasion he let out four ale-house quarts of matter, "for seeing an ale-house quart in the room I had the curiosity to measure it". He continues: "Now if you have any inflammation occurring in the cyst of an abscess equal to the surface of a gallon measure it must be productive of more considerable effect on the constitution than when it occurs on a surface equal to that of a four ounce measure." I wonder if Abernethy was right in his belief that tuberculous pus or material is harmful to a patient who by its production responds to the chronic infection we know to be present. A patient came to the out-patient department of St. Bartholomew's about one hundred years after Abernethy gave his lecture. This bonny, rosy-cheeked, fair-haired girl of 17 with sad and wistful blue eyes was accompanied by her worried but indignant mother who thought her daughter was pregnant. The girl had complained of a little backache for two or three months, which her mother felt was a just retribution for her daughter's misbehaviour. Apart from the very large belly, which might have housed twins and hydramnios, there was no evidence of pregnancy and the patient was demonstrated to the Fellowship class and others as having a large parovarian cyst, and this being a gynæcological condition, my chief—a general surgeon—was eager to perform the operation of removal himself. Pre-operative general examination revealed a certain stiffness of the back probably due, it was felt, to the impediment of the enormous abdomen, but a check X-ray revealed small areas of destruction in the contiguous parts of D.V. 12 and L.V.1, with a diminished disc space, but virtually no collapse or kyphosis. My chief decided to remove the large cyst before sending the girl away for treatment for the tuberculous spine. He needed little encouragement to insert a needle first and into the syringe as aspirated typical tuberculous material. He left me to carry on and I shall never forget

aspirating and filling the 20 c.c. syringe several hundred times in two and a half hours. We had no ale-house quart pot available, but we had the curiosity to measure the four gallons of tuberculous material removed. When we had finished there was a typical large psoas abscess on the opposite side. That was in 1928 and since then I have never seen a tuberculous abscess approaching this size. This was an example of a relatively early tuberculous spine with little destruction and an enormous abscess with practically no constitutional disturbance. Why is it that we find some patients with extensive spinal caries and no discernible or small abscesses and others with minimal lesions and large abscesses? Can it be due to anything other than the varying individual response to chronic infection? I have dallied at some length with Abernethy and his methods, because it was nearly a hundred years before the conservative treatment of surgical tuberculosis again became widely advocated and practised.

At about the same time in France, Dupuytren expressed similar views on the chronic abscess when he stated: "There was never any satisfactory relation between the amount of disease affecting the bone in caries of the spine and the extent of the external disorder, for when caries affects a vertebra, the suppuration which is at first confined to the affected bone gradually extends itself." He described the case of a woman who at autopsy was found to have an abscess with complete destruction of the body of the eleventh dorsal vertebra with the bodies of D.V.10 and 12 partially denuded and the seat of superficial caries.

Towards the latter part of the century operations on tuberculous joints became all too common with disastrous results. Billroth in 1878 stated: "During the last ten years I have felt less disposed towards conservative operations for caries and should have amputated far more frequently if the patients or their friends had not objected. However, the antiseptic method has one advantage, namely that in operations such as excision of the hip the immediate results after operation are much better than they used to be under the old systems. Still, treat these wounds as you will, sinuses will be left and the ultimate results will be almost as unsatisfactory as they used to be. The treatment of this terrible affection—vertebral caries—consists principally in keeping the patient in a recumbent position and children are kept lying, generally in the prone position, but Thomas' splints are sometimes used." Billroth envisaged the possibility of attacking surgically the vertebral lesion. "Hitherto it has been found impracticable to extract large sequestra from the vertebral column. It might seem possible to make an incision on one side of the curvature and in this way to extract the sequestra and gouge away the carious parts, but the hæmorrhage cannot be readily controlled and the spinal cord will be exposed to injury. Yet with our advanced knowledge of the treatment of wounds and in face of the unfavourable prognosis I should not blame any surgeon for making the attempt. I remember some years ago to have read something about an operation of this kind which was performed in America but I do not recollect what became of the patient." It is clear that at that time Billroth was not aware of what might one day be achieved by Capener, Seddon, Wilkinson, Macrae and others.

Howard Marsh in 1889 delivered a Hunterian lecture on "Tuberculosis in Some of Its Surgical Aspects". He advocated treatment of surgical tuberculosis by means short of the excisions which were then of too frequent daily occurrence. At the Hip Hospital in Queen Square he advocated consistently the advantage of early and prolonged non-operative treatment and of traction for tuberculous disease of the hip and said: "The weight should be as small as is consistent with its purpose of relieving pain and preventing or removing distortion; so that it is desirable to diminish the amount as symptoms subside and not to continue to employ a heavy weight after it has become unnecessary to do so." However, generally, patients were allowed to go to the seaside wearing ambulant splints, suppuration was regarded as a normal and inevitable part of the disease, abscesses were opened and treated by poultices, amputations were common and the patients frequently died of amyloid disease. Those who survived had gross joint destruction with deformity, very limited joint movement, and great shortening of the affected limb.

In 1913 the *Practitioner* published a Symposium on Tuberculosis and the greatest discussion surrounded the use and abuse of tuberculin and of its potential value as a therapeutic agent. Pearce Gould stated "We may say that all cases of tuberculosis must be treated medically and that the need for medical measures is never more urgent than when a case requires some operative interference to complete the cure." He advocated surgical removal of tuberculous foci in bone which had not cleared up with general measures, but a sufficiently free opening must be made and failures would result from attempts to scrape away a large area of disease through a puncture—"it would be as sensible to ask a housemaid to clean out a room through the keyhole in the door!" Robert Jones in an invaluable contribution stressed the necessity for mechanical fixation. He wrote: "In recent years, I have on many occasions been called upon to deal with tuberculous disease of joints and of the spine, in cases in which an enthusiastic believer in the efficacy of tuberculin has entirely omitted any form of protective fixation, and it is therefore necessary to express my strong conviction that this is a serious error. The neglect of protective fixation is unfair to tuberculin treatment, for repeated injuries to the

diseased structures caused by movement delay, if they do not prevent, the beneficial action of the immunizing treatment." Robert Jones made no attempt to scrape out the tuberculous lesions "for I have too great a dread of the terrors of mixed infection and set excision of a joint for tuberculosis is unknown in my practice". Can we not to-day substitute for tuberculin, streptomycin, I.N.A.H. and other antibiotics and say with Robert Jones that the neglect of the protective fixation of tuberculous joints is unfair to treatment by antibiotics?

I need not dwell on the patterns of non-pulmonary tuberculosis nor on the general and mechanical methods of treatment elaborated during the first half of this century for they are well known, and if I pay tribute to the outstanding work of Robert Jones, Gauvain, Pugh, Girdlestone and Brittain in this country, this is not to say that I do not fully appreciate the considerable contributions made by many others. The orthopædic lesion secondary to a primary focus was regarded as a local manifestation of a general bacillæmic disease and demanded both general and local conservative treatment. Patients remained for long periods in special hospitals and when the lesion became quiescent protective surgery was frequently performed. During the past ten years, the outlook and patterns have changed materially with the advent of antibiotics. Penicillin was of some value in controlling secondary infection to a large extent, but it was streptomycin that made a direct assault on the local disease safe and possible. The emergence of resistant strains of tubercle bacilli was avoided to a large extent by a combination of streptomycin, PAS and I.N.A.H., and it is a moot point as to whether or not this therapy should be reserved for critical phases and episodes in the natural history of the disease.

Value of Antibiotics

(1) During the bacillæmic stage to assist the patient in coping with the general infection and thereby avoiding multiple tuberculous lesions.

(2) The centre of a tuberculous lesion may be caseous and, as the result of tuberculous endarteritis, have no blood supply. Systemic antibiotics cannot reach the core of disease, but in the surrounding hyperæmic zone can contain the local disease and limit the local spread of infection and destruction.

(3) Long-standing sinuses may heal soundly following systemic administration and local instillations.

(4) Direct attack on the tuberculous lesion is now possible under the antibiotic umbrella and the dread of dissemination is no longer a haunting spectre.

(5) The length of treatment has been greatly curtailed and is generally half or even less of what it was before. Patients are in and out of hospital far more quickly, the turnover of patients is more rapid and the number of in-patients and the waiting lists have fallen dramatically.

LORD MAYOR TRELOAR ORTHOPÆDIC HOSPITAL

STATISTICS ON TUBERCULOSIS

1932: Twenty-five years ago over 50% of patients were tuberculous—
Admitted 26 spines, 66 hips, 14 knees and 50 other tuberculous lesions.

1937: Twenty years ago about 50% of patients were tuberculous—
Admitted 30 spines, 50 hips, 10 knees and 80 other tuberculous lesions.

1957: *February*. 25 children with non-pulmonary tuberculosis.
" 20 adults " "
Waiting list of 5 patients.

Surgery of the Local Lesion

It is now possible to operate on the infected bone or joint without being unduly concerned about the tuberculous nature of the infection and for example dealing directly with caries of the vertebral bodies, as envisaged by Billroth, has become a reality as the result of strict aseptic technique, superb anæsthesia and antibiotic cover. Tuberculous cavities are curetted, sequestra removed and gross tuberculous lesions can be excised, as in partial synovectomy of the hip. Antibiotics can be applied locally to the exposed tuberculous lesion, and systemic antibiotics become more effective as the result of the reactive hyperæmia following the surgical assault. The processes of repair can be enhanced by the insertion of bone chips ground in streptomycin into tuberculous cavities or denuded joints. Temporary internal fixation of joints by nails can if desired be used with impunity. It is not suggested that radical and difficult surgical procedures should be undertaken lightly, but that surgery has been made safe by antibiotics, by blood transfusion, by expert anæsthesia, and above all by a rigid compliance with the long-established principles of a sound aseptic technique.

The management of the local tuberculous lesion may thus be summarized:

Tuberculosis of the Hip

(1) General constitutional treatment of the patient with bed rest.
(2) Local treatment by immobilization and traction.
(3) Confirmation of diagnosis by biopsy.
(4) Antibiotic therapy—adequate and prolonged.
(5) Partial synovectomy where indicated and local antibiotics. The ideal end-result is a hip with a good and safe range of movement.
(6) Curettage of the juxta- but extra-articular lesion and insertion of bone chips.
(7) Displacement trochanteric osteotomy if response to therapy is inadequate.
(8) Arthrodesis when joint movement is inadequate and not safe. When joint destruction is gross, the tuberculous debris may be removed, iliac bone chips and graft inserted and temporary fixation secured by the insertion of a Smith-Petersen arthrodesis nail. Otherwise extra-articular ischio-femoral arthrodesis using the technique described by Foley. Intra-articular arthrodesis is no more difficult or dangerous than it is in the tuberculous knee.
(9) If the great trochanter is involved, excision of the trochanter and the overlying abscess.

Tuberculosis of the Spine

(1) General treatment and bed rest.
(2) Local immobilization and mechanical treatment.
(3) Confirmation of the diagnosis by Mantoux tests, the bacteriology of aspirated tuberculous material and sometimes by exploratory curettage.
(4) Systemic antibiotic therapy.
(5) In the quiescent stage when consolidated collapse has occurred, posterior spinal fusion if necessary, for example in the cervical spine.
(6) Aspiration of tuberculous abscesses where possible and repeated only as frequently as is necessary.
(7) Drainage and lavage of the perivertebral thoracic abscess. Macrae has stressed that this can only be done effectively by a bilateral approach and through-and-through irrigation. It has been suggested that this procedure may limit the spread of tuberculous disease to neighbouring vertebræ.
(8) Evacuation of tuberculous cavities in the vertebral bodies. Tomograms particularly in the cervico-dorsal region are invaluable in determining whether this procedure is desirable in the absence of paraplegia. In the mid-lumbar region the bodies can readily be exposed by an antero-lateral extra-peritoneal approach, tuberculous debris and the remains of any intervening disc are removed, healthy firm bone is exposed, and bone chips and streptomycin are inserted under compression and an anterior spinal fusion obtained.
(9) The management of Pott's paraplegia is adequately described in the excellent papers and monograph to which I have already referred.

Little need be said of the tuberculous lesions of other bones and joints. When gross destruction occurs in the tuberculous shoulder, intra-articular arthrodesis by joint excision, insertion of bone chips and temporary fixation with a short Smith-Petersen nail may be performed.

In the tuberculous knee a good range of movement may result with or without synovectomy, but if gross destruction is present compression arthrodesis is indicated.

Satisfactory results may be obtained in the tuberculous tarsus, by curettage and excision with the insertion of bone chips.

Relative Merits of Surgery and Antibiotics

(1) Radical operative measures have followed so closely on the advent of antibiotics that it is difficult to assess the value of each. As patients with almost identical lesions differ in their response, it is no answer to treat one patient by antibiotics alone and the next with antibiotics and surgery. However, so far as possible the alternatives should be used on like and strictly comparable cases and not indiscriminately on alternate patients.

(2) Antibiotics may be used without surgery in the hyperæmic lesions, and if surgery is employed its value lies largely in improving the blood supply to the affected part.

(3) Does the perivertebral abscess cause spread of tuberculous disease to neighbouring vertebral bodies or are the radiographic changes seen consistent with the results of intermittent mechanical pressure seen in the aneurysm phenomenon? One or more vertebræ are involved initially due to hæmatogenous or bacillæmic infection. When several contiguous vertebræ become involved, resulting in due course in a severe rounded kyphos, is involvement due to further hæmatogenous infection or to involvement because of the stripping effect of the abscess? Are all the vertebræ showing radiological erosion tuberculous or do some exhibit the aneurysm phenomenon? Does widespread involvement occur without the presence of an obvious abscess? If as is probable the perivertebral thoracic abscess can infect other vertebræ it should be evacuated and irrigated, but does this procedure

prevent an abscess reforming? In the presence of active tuberculous disease is not an abscess evidence of satisfactory tissue reaction? However, whatever its precise pathological effect, I think I am persuaded that the tense thoracic perivertebral abscess should be drained, even in the absence of paraplegia, in order to limit the spread of pathological and radiological changes.

(4) Tuberculous cavities in bone if accessible should be evacuated and the healing process should usually be assisted by the insertion of bone chips.

(5) The only safe end-results of tuberculous joints are freely movable joints or those in which there is sound bony ankylosis.

The Future

(1) In the large cities bovine tuberculosis has been largely eradicated as the result of the production of safe milk.

(2) Mass radiography is resulting in the earlier discovery of patients with open lesions, who are treated more radically, so that the sum total of infective persons is becoming far less in this country if not globally. Sanatoria have empty beds and waiting lists are almost non-existent.

(3) BCG inoculations will protect susceptibles and thereby diminish still further the potential transmitters of disease.

(4) The value of PAS, I.N.A.H. and of streptomycin and its derivatives and associates is outstanding. The danger lies in the emergence of resistant strains and instances have been reported of patients who when discovered initially are resistant to some of the therapeutic agents if not to all. The question must be posed: Should antibiotics be administered to suspected cases without biopsy and adequately and indiscriminately to all proven cases or should they be reserved for critical periods and phases in the natural history of the disease, e.g. in the bacillæmic stage, for operative cases, and for generalized miliary tuberculosis? The present trend to curtail the dose and continue for many months or for a year or longer may prove satisfactory.

(5) The principles of treatment learned and practised laboriously over the years must not be forgotten. General conservative treatment is more necessary now than ever in the past and combined with local treatment is more likely to produce satisfactory end-results. Although the length of hospital treatment is now largely curtailed the need for specialist long-stay hospitals is greater than ever.

(6) Is it too much to hope and expect that non-respiratory tuberculosis will in the foreseeable future become as uncommon in its devastating effects as rickets, chronic osteomyelitis and the gumma?

(7) Historical surveys reveal to us the apparent progress that has been made in the past, but also serve as a reminder of our limitations and as a guide to the future. The historian a thousand years hence will regard our knowledge and practice of orthopædics as very primitive and incomplete. Preventive medicine may be such that orthopædic surgery as we know it to-day may not exist. Crippling diseases may be stamped out, congenital defects and deformities may be preventable and the immediate treatment of accidents and injuries may be so good that subsequent orthopædic care will be unnecessary.

[*June* 15, 1957]

THE Summer Meeting of the Section of Orthopædics took place at Lord Mayor Treloar College, Near Alton, and afterwards at Lord Mayor Treloar Hospital.

Cases were shown and the following papers were read:

The Treatment of the Cavus Foot by Flexor to Extensor Toe Tendon Transplants Combined with other Procedures.—Sq. Ldr. R. W. POVEY.

Dislocation of the Patella and Its Relation to Chondromalacia Patellæ.—Mr. H. H. LANGSTON.

Review of Cases of Genu Valgum Treated by Stapling.—Mr. J. D. WILSON.

Some Observations on the Mechanical Problems of the Artificial Hip.—Mr. E. H. J. SMITH.

Operative Treatment of the Tuberculous Cervical and Dorsal Spine.—Mr. D. E. MACRAE.

Some Radiological Problems from the Middle East.—Dr. R. O. MURRAY.

Section of General Practice

President—JOHN H. HUNT, M.A., D.M.

[*April* 17, 1957]

DISCUSSION: EYES IN GENERAL PRACTICE

Dr. John Fry: A general practitioner finds considerable difficulty in the interpretation of the many intricacies concerning diseases of the eyes and he constantly looks to his consultant colleagues for their help and advice.

These difficulties appear to arise from a lack of adequate teaching on the subject, the only teaching given being a few sessions during the already overcrowded syllabus of the undergraduate; from a lack of material in practice on which to develop one's experience, for eye conditions account for only 4–5% of all work in general practice and the vast majority of these are relatively minor and self-curing conditions. Until recently there has been a sad lack of literature on the subject specifically for the general practitioner. We now have available two excellent books by Perkins and Hansell (1957) and Jackson (1957).

The importance of eye disorders need hardly be stressed both as local affections and as part of a more generalized disease process as in hypertension, diabetes and renal disease. The family doctor should endeavour to acquire experience and proficiency in the standard methods of diagnosis and be able to apply to his findings a basic knowledge of pathology in order to provide a correct diagnosis and suitable treatment.

By way of introduction I shall discuss the proportion and types of eye disorders seen in a typical suburban practice in S.E. London over a period of one year (Table I).

TABLE I.—EYE CONDITIONS IN A PRACTICE IN ONE YEAR

Condition	No.	% of total number of patients	Referred to hospital
Acute infection	136	68%	4
Accident and foreign body	30	15%	2
Inflammations	6	3%	3
Squint	14	7%	14
Others	14	7%	10
	200	100%	33 (16·5%)

These patients suffering from disorders of the eyes represent around 5% of all patients seen during the year. In addition, there were some 50 patients who required certification for the purposes of refraction.

By far the most frequent type of eye condition met with in general practice is some superficial *acute infection* such as conjunctivitis, blepharitis or styes—accounting for 68% of the total. Management rarely presents any major problems since almost all will settle spontaneously without treatment. Antibiotics, either local or systemic, are required in only a minority of cases.

In my suburban practice *injuries* to the eyes accounted for only 15% of all the eye disorders—this figure will probably be greater in industrial areas.

Inflammations of the uveal tract, so common in hospital practice were responsible for only 3% of my cases. Children with *squints* were seen almost twice as frequently.

Others were a mixed group with various degenerative conditions predominating.

In Table I can be seen the proportion of cases referred to the consultant. The family

doctor is able to cope with over 80% of all the eye conditions that he meets and those that he does have to refer do not represent the most common groups.

If the lack of confidence of the family doctor in dealing adequately and correctly with eye disorders is to be remedied steps should be taken to organize and make available suitable simple postgraduate courses designed specifically for the G.P. dealing with such subjects as principles of pathology, diagnostic methods in general practice, principles of therapy and especially the use of antibiotics and the cortico-steroids in eye disorders.

REFERENCES

PERKINS, E. S., and HANSELL, P. (1957) An Atlas of Diseases of the Eye. London.
JACKSON, C. R. S. (1957) The Eye in General Practice. London.

Mr. Joseph Minton:

The most common eye conditions referred nowadays by general practitioners to the ophthalmic departments are: (1) Inflammations of the cornea. (2) Episcleritis. (3) Iritis and iridocyclitis.

Since the introduction of sulphonamides and antibiotics conjunctivitis has usually been successfully treated by the general practitioner. Complications following severe conjunctivitis, such as corneal ulcers and superficial punctate keratitis, are often sent for further treatment to the ophthalmologists.



FIG. 1.



FIG. 2.

FIG. 1.—*Herpes Zoster Ophthalmicus.*—This boy, aged 10, was suffering from acute left herpes zoster ophthalmicus with the usual involvement of the left cornea.

Hydrocortisone with chloramphenicol eye drops and ointment were used as soon as the condition was diagnosed. The cornea cleared within a few weeks, leaving no scarring.

The boy now has good vision in the left eye.

FIG. 2.—*Episcleritis.*—This patient is suffering from episcleritis of the temporal part of the right eye. The patient was complaining of severe pain of the right eye. The œdematous patch on the temporal side of the cornea was red.

Hydrocortisone drops and ointment were prescribed and the eye improved two weeks after the commencement of treatment. The patient is advised to repeat the same treatment if the inflammation recurs, which is often the case.

Cortisone, hydrocortisone and other allied anti-inflammatory drugs have been of the greatest value in the treatment of inflammatory eye diseases. The cases in which cortisone or hydrocortisone should be used are:

(1) Episcleritis.
(2) Phlyctenular keratitis and keratoconjunctivitis.
(3) Superficial and interstitial keratitis.
(4) Rosacea keratitis.
(5) Keratitis following herpes zoster ophthalmicus.
(6) Keratoconjunctivitis sicca. (This condition is often associated with rheumatoid arthritis and erythema multiforme.)
(7) Iritis and iridocyclitis.
(8) Choroiditis.

Iritis and iridocyclitis should be treated with cortisone or hydrocortisone at the earliest stage of the disease. As soon as the diagnosis of iritis is made, the patient should be given a subconjunctival injection of hydrocortisone (½ c.c.) combined with atropine. The patient is advised to use hydrocortisone eye drops three times daily and hydrocortisone eye ointment twice daily. It is necessary to continue with these preparations for a long period. The treatment should not be stopped before all the signs of inflammation (iritis and iridocyclitis or keratitis) disappear.

Choroiditis (posterior uveitis) rarely responds to cortisone or hydrocortisone eye drops. In these cases systemic ACTH should be given for at least two or three weeks. Systemic administration of prednisolone (delta-hydrocortisone) in a dose of three 5 mg. tablets daily is nowadays used with great success in the treatment of choroiditis and iridocyclitis. To offset potassium loss, which is usual during the treatment with cortisone or its derivatives, the patient should also take 3·0 grams of potassium chloride daily. The blood pressure is checked twice weekly and the urine should be examined twice weekly to exclude glycosuria. The patient is advised to take a salt-free, high protein diet, and to reduce his fluid intake. The quantity of prednisolone is gradually reduced. In cases of choroiditis or severe iridocyclitis at least six weeks' treatment with prednisolone is necessary.

Herpes Zoster Ophthalmicus is often associated with corneal complications (keratitis with loss of sensation of the cornea). In my experience the early administration of hydrocortisone drops and ointment combined with chloramphenicol or neomycin for at least six to twelve weeks prevents severe corneal complications. Systemic administration of penicillin is most helpful because it deals with the secondary infection of the herpes vesicles.

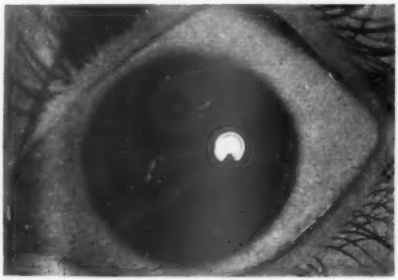


FIG. 3.



FIG. 4.

FIG. 3.—*Uveitis and Keratitis of Left Eye.*—This patient, aged 11, is suffering from uveitis (iridocyclitis and choroiditis) of both eyes associated with Still's disease. Seven years ago she developed uveitis of the right eye. Local treatment with cortisone (subconjunctival injections and drops and ointment) did not improve the vision of the right eye. She can only see shadows of large objects with this eye.

Two years ago she developed uveitis of the left eye which caused loss of vision. She was then treated with systemic ACTH and the vision of the left eye improved to 6/12.

A year ago she developed Still's disease (juvenile rheumatoid arthritis) which again caused acute uveitis of the left eye with loss of vision. Since October 1956 she has been treated with deltahydrocortisone tablets (Prednisolone). This treatment again restored the vision of the left eye to 6/18. Her eyes are now not inflamed. She is still having two Prednisolone tablets daily.

FIG. 4.—*Acute Choroiditis of Right Eye* (*Retinal Photograph*).—This patient, aged 32, was suffering from acute choroiditis of the right eye two years ago. All investigations were negative. He was treated as an in-patient at the Hampstead General Hospital.

Intramuscular injections of ACTH gel 60 units daily were administered for three weeks. The vision of the right eye, which before treatment was very poor (6/36), improved rapidly to 6/6. Exudates disappeared. Vision normal within three weeks. Patient seen May 1957 when no scarring or pigmentary changes could be found in the retina.

Mr. [illegible] A. Williamson-Noble:

Much can be learnt in General Practice by simple methods of examining the eyes.

(1) *External examination.*—Direct the patient to look up, evert the lower lid by pulling it down and examine its inner surface for evidence of conjunctivitis. With the lid still in this position, the inferior lacrimal punctum will be exposed and pressure over the lacrimal sac will cause pus or mucus to escape if infection is present. The sac lies deep to the internal

palpebral ligament and so can easily be located. The upper lid can then be everted by one of the usual methods if a foreign body is suspected and a rough estimate made of the intra-ocular pressure by palpating the globe through the uneverted lid with the index finger of each hand, the middle fingers resting on the patient's forehead.

With the patient looking straight ahead, pupil reactions and ocular movements can be tested. A good idea can be obtained of the integrity or otherwise, of the corneal surface by observing the reflection in it of a window as the patient looks in various directions and noting whether there is any distortion. If uniocular conjunctivitis should be found, a foreign body, misplaced lashes, an inturned lower lid or lacrimal sac may be the cause.

(2) *Functional examination.*—Subnormal visual acuity. If the patient can see further down the test card when looking through a pinhole in a piece of cardboard, an error of refraction can be held partly, if not wholly, responsible.

Visual field. Its extent can be estimated by the confrontation method. In this the examiner stands opposite the patient and directs her to cover say her right eye and look with her left into his right eye. He can then compare her field with his own by bringing in a small white object from the periphery. A white-headed hat-pin is probably the best to use, but failing this, a piece of white paper $\frac{1}{2}$ in. square, impaled between the points of the nib of a pen can be used. The target should be held so that it is the first thing to come into view and is equidistant from patient and examiner.

For central field defects, produced say by some retinal disturbance, Amsler's chart, consisting of squared paper printed in white on black is invaluable; distortion or absence of some of the squares being noted in cases of disease (Neame and Williamson-Noble, 1956).

(3) *Ophthalmoscopy.*—It is a good thing to start with a +12 lens in the sight hole, gradually decreasing its strength until the fundus is visible. In this way, opacities in the cornea (keratic precipitates) lens and vitreous can be detected. In the case of patients with high myopia or astigmatism the fundus is seen more clearly if the patients wear their glasses, tilting them forward slightly to displace the reflection of the ophthalmoscope light.

Much more can be seen through a dilated pupil. If the examiner is unwilling to take the remote risk of precipitating glaucoma by using a drop of homatropine and cocaine, quite good dilatation can occur about half an hour after instillation of two drops of 4% cocaine hydrochloride with a five minutes interval between them. Although diagnosis of eye disease is the more important part of general practice and in this respect, the careful taking of a history can be invaluable, there are at least two emergencies whose treatment should be mentioned.

The first is sudden loss of vision in one eye. The majority of such cases are due to obstruction of the central retinal artery and can be diagnosed by the ophthalmoscope. If seen soon after onset, firm pressure on the eyeball with the fingers over the closed lids for five seconds followed by sudden release, may result in displacement of the clot or embolus from the main artery into one of its branches. The manœuvre should be repeated every ten or fifteen seconds for at least thirty minutes if improvement in vision does not occur before this.

The second is acute glaucoma. In this, a drop of oily eserine 1% should be instilled into the eye every five minutes for two to four hours and then continued four hourly. This should be accompanied by oral administration of diamox 500 mg. followed by 250 mg. four hourly for twenty-four hours and then eight-hourly.

REFERENCE

NEAME, H., and WILLIAMSON-NOBLE, F. A. (1956) Handbook of Ophthalmology, London.

Mr. J. P. F. Lloyd showed a film entitled: "What the General Practitioner should know about Glaucoma." This film was made some years ago by the National Association for the Prevention of Blindness, Inc., in an effort to draw the attention of medical men to the magnitude and complexity of the glaucoma problem. It contains some most graphic illustrations of the mechanism of the disease and some suggestions which should be very useful to general practitioners in England in looking out for this condition in their patients.

Section of Physical Medicine

President—A. C. BOYLE, M.D., M.R.C.P.

[*April* 10, 1957]

DISCUSSION ON REFERRED PAIN

Dr. G. Weddell (Department of Anatomy, University of Oxford):

Referred Pain in Relation to the Mechanism of Common Sensibility

The neuro-anatomist is faced with unexpectedly difficult problems when he starts to analyse the structural arrangement of the peripheral sensory nervous system in terms of common sensation. To determine, for instance, whether a particular nerve terminal is related to a particular sensation such as pain, appears to be a straightforward question to which it should be possible either to give or to find an answer. But this is not so, for the word pain has many connotations. This constitutes a serious dilemma, for the framework of terminological definition within which the academic neurologist tries to work is quite different from that restricting the clinician. The clinician must necessarily assume a set of definitions which are far less stringent than those employed by the academic neurologist for he has to analyse the symptoms reported by patients.

Advancement of knowledge, however, must ultimately depend upon a convergence, not further divergence, between these two extremes.

When I use the word "pain" in this discussion, I mean the sensations reported by healthy resting subjects when their skin is either severely crushed or burnt. Further I would accept the sensations reported by patients either during an attack of renal colic or following a movement which tears and displaces part of the medial semilunar cartilage in a knee-joint as coming within my definition of pain. By contrast, I do not accept as pain (but only in relation to the restricted definition I have adopted) a sensation reported as agony but engendered solely by grief. By this I do *not* mean that I disbelieve what the patient says but that, for the purposes of this discussion, I do not accept such complaints as coming within my definition of the term "pain", although I am only too well aware that grief may modify the sensations evoked by physical stimuli which are not usually reported as pain.

Having defined pain, I, in the role of a neuro-anatomist, must first ask myself whether or not there is evidence that pain is subserved by a specific set of peripheral sensory nerves and terminals which, in turn, come into relationship with specific neurons and tend to be segregated in specific pathways within the central nervous system. This is the commonly-accepted theory and there are some facts which can be cited in its support. For instance, reports of pain in the hands cannot be evoked by any means whatever from certain patients known to be suffering from syringomyelia; the same is true for the leg following a successful antero-lateral cordotomy. Yet, in both cases the patients usually report that touch sensibility from the affected parts is unimpaired. Observations of the effect on sensibility of infiltrating tissues, in particular skin, with local anæsthetics also seem to support the idea that there are specific pain nerves, for among other things, pain sensibility is apparently abolished before touch.

The facts I have just referred to, however, do no more than support the hypothesis that there are specific pain nerves. Recently a number of new observations have been reported which suggest that this may not be the case. For instance, Sinclair *et al.* (1952), Hagen *et al.* (1953), Weddell, Palmer and Pallie (1955) and Dastur (1955) have shown that in hairy skin which covers by far the greater part of the body, there are no complex circumscribed nerve endings, such as Meissner corpuscles, Krause end-bulbs and so forth. The nerves either terminate in a highly complicated manner in relation to hairs, or in the form of widespread arborizations of fine, freely-ending filaments, which interweave and overlap with one another, i.e. so-called free nerve endings. This observation alone destroys von Frey's theory that the primary modalities of common sensation, i.e. touch, warmth, cold and pain, are each subserved by morphologically specific nerve terminals, at least as regards hairy skin. In hairy skin, free nerve endings must subserve the modes of warmth and cold, for the terminals ending in relation to the hairs do not discharge when the skin is either warmed or cooled. It is, of course, generally accepted that they subserve pain. It can nevertheless be argued that the free nerve endings, if not morphologically specific, are physiologically specific. The evidence in favour of this view (Zotterman, 1953), although limited and of an indirect nature, cannot be disregarded. But the evidence against it is increasing in amount, it is derived from a number of different sources and the new theory which emerges provides a useful and satisfying working hypothesis. None of the evidence is direct, however, and the theory is still, scientifically speaking, just a good idea.

The evidence against the theory that there are specific pain nerves is both of an anatomical and physiological nature and I shall try to summarize it as briefly and succinctly as possible. It has been shown by Lele (1954) that reports of warmth and cold are never evoked when fine quartz[1] needles are inserted through the skin, although reports of touch, prick, itch and tickle were aroused from every subject in due course. This alone suggests that the mechanism of thermal sensibility is more complex than has been suggested. Further, Lele *et al.* (1954) have shown that reports of warmth and cold are dependent upon the transfer of heat to and from the skin respectively; they are not related to the absolute temperature of the skin. Together, these observations suggest that thermal sensibility is in some way connected with the *pattern* of the discharge evoked from the skin and not just due to a discharge from modality specific endings. Another series of observations, in this case quantitative and anatomical in nature, lends support to this idea. It has been shown that in the rabbit ear (qualitatively man parallels the rabbit) the hairs not only form a highly complex and continuously variable pattern but their mode of innervation is equally complex. The striking points which emerged were that every hair is multiple-innervated, being subserved by at least two dorsal root axons of different diameters. The average number subserving a single hair is around six and guard hairs may be subserved by as many as twenty. Moreover, there is no more than one dorsal root axon available for every 20 hairs and the hairs which it subserves may be scattered over a relatively large area. It has also been calculated that each and every dorsal root axon could be caused to discharge simultaneously if a selection of no more than one-quarter of the total number of hairs in the ear was stimulated (Weddell, Taylor and Williams, 1955).

These observations can only mean that messages which, for example, enable hairs to be accurately localized are, as it were, coded for transmission and reach the central nervous system as trains of spatially and temporally dispersed action potentials where they are presumably decoded. There can be no question of each hair having a private and exclusive line along which to pass messages centrally.

I believe that free nerve endings and the nerves subserving them in the skin are arranged in a similar kind of way and I shall now state the evidence in favour of this belief, leaving my readers to judge whether they will accept this new theory regarding the mechanism of pain.

In the first place, the number of sensory nerves subserving free nerve endings in the skin of the rabbit ear cannot be more than about 1,500 and, as regards axon diameter, the fibres are scattered in a random way in the nerve bundles at the base of the ear. This arrangement naturally suggested to me that information from free nerve endings is also coded for transmission to the central nervous system by way of a minimum number of parent axons. Unfortunately, we found it impossible with the methods at present at our disposal to analyse the matter any further in the rabbit ear.

After taking stock, we decided to approach the problem from a fresh angle. We asked ourselves where in man is there an area of integument subserved solely by free nerve endings and which, when appropriately stimulated, evokes reports referable to each of the four primary modes of common sensation? We soon remembered that it is generally agreed and that we had confirmed that the human cornea contains only free nerve endings; incidentally, it is also avascular and free from autonomic nerve fibres. At the same time, we also remembered that it is generally accepted that pain is the only sensation ever reported when the cornea is effectively stimulated. Nevertheless, we decided to reinvestigate this problem for from what we now knew about hairy skin, and from what we read in the literature concerning corneal sensibility, it seemed to us that this belief in its restricted nature was possibly not founded on a firm scientific basis.

Our suspicion proved correct for we have now been able to show that sensations in all four primary sensory modes can be evoked when the cornea is suitably stimulated (Lele and Weddell, 1956). Reports to the contrary we have been able to trace to the fact that few observers in their experiments used appropriate stimuli; for instance, the fact that reports of warmth did not follow stimulation of the cornea with horse hairs which had been dipped in hot water were considered to be conclusive. But hairs have no thermal capacity and could not have transferred heat to the cornea. By contrast, we found (among other things) that a copper rod of reasonable diameter heated to a temperature 1° C. above that of the surface of the cornea was invariably reported as being warm.

Having established that the cornea in respect of common sensibility behaves like the skin, clearly the next step was to record action potentials from single ciliary nerve fibres subserving the cornea, to determine the size and patterned relationship of the free nerve endings to one another and to determine whether individual endings were modality specific. In other words, if stimuli equivalent to those reported as touch, warmth, cold and pain evoked action potentials in specific groups of nerve fibres and not in others.

It has not so far proved possible for us to carry out such an experiment in man. For

[1]Fine quartz needles (20 μ) have a very low thermal capacity.

ately however, as far as we could see, the cornea is a tissue which does not differ fundamentally from species to species (Zander and Weddell, 1951). We therefore carried out the investigations which I have just outlined in the cat. The answer was unequivocal. The free nerve endings are arranged in a complex pattern and those derived from widely separated parent axons overlap and interweave extensively. Moreover, the number of parent axons which supply the cornea of the cat is less than 1,000. Finally, it is clear that free nerve terminals in the cat's cornea can all transduce more than one kind of stimulus. For instance, all of them transduced stimuli reported as either touch or pain when applied to the human cornea and all but two (in more than 200 which have been investigated) transduced stimuli of heat transfer in either direction; some, however, had a lower threshold for heat flux in a particular direction. The activity evoked by brushing, heat transfer and "injury" in the case of a particular ending were of different patterns and time courses but it was not possible to distinguish any significant difference in the case of positive ("warmth") and negative ("cold") heat transfer respectively. However, stimuli which damaged the cornea invariably gave rise to a large number of action potentials which often lasted for an indefinite period (undiminished activity for up to 10 minutes). These observations provide no direct evidence as to the mechanism of common sensation in man but they are highly suggestive and it is tempting to speculate that pain *as I have defined it on page 581* is reported when the number of impulses from any or all the free nerve endings in a given zone rises excessively, is maintained, evokes excessive excitation centrally and reaches the "pain centre", i.e. pain is an excitatory space/time impulse pattern (which reaches the appropriate centre without being blocked *en route*) from terminals which, when suitably stimulated, can give rise to reports of sensations related to other sensory modes.

One of the satisfying things about this theory is that it provides a mechanism which can account for the large number of different kinds of pain about which patients complain and which the doctor uses as a means of diagnosis. In a sense, it makes nonsense of my initial definition for, if you accept the implications of the theory which I have erected, there is no room for such a restrictive practice.

Referred Pain

I have discussed pain at some length, as opposed to referred pain, for I felt that it was impossible to ignore any work which may lead us to modify our views concerning the nature of the activity reaching the central nervous system from the periphery which consistently evokes reports of pain.

The literature is full of speculation as to the mechanism of referred pain and the phenomena associated with it; i.e. cutaneous hyperalgesia, superficial and deep tenderness and a local muscular spasm. However, the numerous shades of opinion which have been expressed are usually resolved into two opposing theories, each of which is manifestly supported by a number of verifiable facts; curiously enough, no one seems willing to accept the possibility that more than one mechanism is involved in any particular case.

One theory is that the phenomena of referred pain are due to events taking place in the periphery and the other, that the mechanism responsible is located in the central nervous system. Neither theory, however, can be regarded as exclusive on the facts available.

The evidence in favour of the theory that the phenomena of referred pain are due to events taking place in the periphery was set out fully by Sinclair *et al.* in 1948 but even they were persuaded that it was desirable to construct yet another hypothesis based on a single mechanism to account for the divergent views which had been expressed previously. They were, however, careful to state that their hypothesis might well require extension and amplification, and, in particular, to account for the reference of pain and associated phenomena to distal segments. Their chief objective was to emphasize that no theory that is put forward can afford to ignore the possibility that axon branching in the sensory (particularly peripheral) pathways is responsible, at least in part, for the phenomena of referred pain.

The theory they put forward (which is in fact an extended and amplified version of, and includes, those which have been put forward previously) rests on a basis of currently accepted anatomy and physiology and it is certainly capable of explaining many of the numerous, sometimes divergent, observations which have been made on the reference of pain from both somatic and visceral structures. They envisage a mechanism based on the existence of a small percentage of parent dorsal root axons having a number of peripheral branches, one passing up from the site of origin of the disturbance, i.e. gut or deep somatic structures, another from the area of skin to which the pain is referred, yet another arising in adjacent somatic musculature and so on. The theory is summarized in its simplest form in Fig. 1.

Such an arrangement, it is suggested, could operate in two ways: first, by leading to a misrepresentation by the central nervous system of the true origin of the pain impulses; second, by the liberation of chemical substances (Lewis, 1942) at the terminals in the region where the pain is experienced, which would in turn stimulate interweaving and overlapping terminals

subserving neighbouring parent axons, thus giving rise to secondary pain impulses actually having origin in the periphery. In any given case, both mechanisms might be concerned. To explain cutaneous hyperalgesia, the first is considered as being initially more important than the second, but the second as increasing in importance with time and in the later stages preponderating.

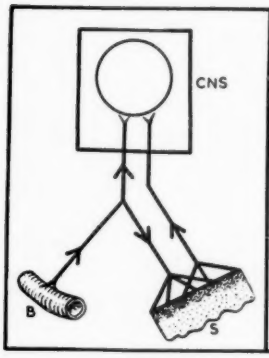


FIG. 1.

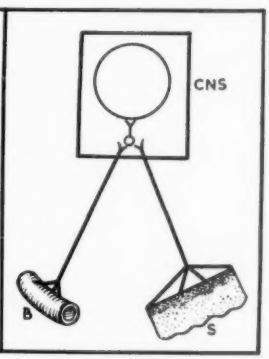


FIG. 2.

The phenomenon of misreference is explained as follows; the nerve terminals at B (Fig. 1), which may be either in the gut or any deep somatic tissue, lie in positions where they are protected from stimuli which impinge on the surface of the body and thus seldom, if ever, discharge any impulses. Moreover, there are very few of them and each is spread over a very much larger area than the terminals in S which represents the cutaneous site of reference; this suggests that a relatively extensive disturbance would be necessary to discharge them (Feindel *et al.*, 1948; Schofield, 1957). These two factors ensure that, under normal circumstances, the preponderance of impulses reaching the spinal cord will arise (together with impulses from neighbouring axons) in the skin arm of the axon. Hence the brain comes to refer all impulses reaching the cord along the parent axon to the skin. It can likewise be argued that antidromic impulses, passing down other arms of the axon, when the skin is stimulated, would be spread over such wide areas that the local concentration of chemical substances liberated would not normally be high enough to give rise to any signs or symptoms. Incidentally, this would perhaps explain why, in counter-irritation, it has been found necessary to resort to skin blistering in order to obtain an effective response.

Perhaps the greatest weakness of the theory is that, although parent axons, having two peripheral limbs, each passing along a different nerve trunk, are known to exist in amphibia (Adrian *et al.*, 1931), in fish (Wernoe, 1925, 1927) and probably also to exist in mammals (Dogiel, 1896; Lloyd, 1944), the position with regard to man is just unknown.

In my view, another weakness is the explanation which is put forward to explain referred tenderness, for it is necessary to assume that antidromic impulses produce chemical substances which, at first, stimulate the nerve endings and later *damage* them, if reports that pain can sometimes be relieved by anæsthetizing the area of reference are to be explained. In other words, it has to be assumed that pain and tenderness in the area of reference are, at first, as it were, an illusion, but rapidly become a reality which may persist independently for some time after the original cause has been removed.

You will probably have noticed that the theory as formulated by Sinclair *et al.* in 1948 assumes the existence of a specific set of pain nerves operating more or less within an all-or-nothing framework. If, however, you adopt the hypothesis that it is the pattern of discharge from free nerve endings which determines the report which is evoked, the particular objection to which I have just been referring loses some of its force for it is then only necessary to assume that pain will be reported when the total number of impulses passing along the parent axon rises excessively. The abolition of pain by anæsthetization of the area of reference is then explained on the basis that in some instances this reduces the total impulse frequency in the common parent axon below the threshold necessary to evoke pain, in other cases it does not. On this score, it is no longer necessary (in particular to explain referred tenderness) to assume that terminals in the area of reference are either damaged or that the original cause has ceased to operate.

Thus, it is possible to make out a case in favour of the view that the phenomena of referred pain are at least *in part* explicable on the basis of mechanisms taking place in the periphery. But one must face the fact that it is still not known whether axon branching actually takes place in man in the manner which has been conjectured. Moreover, the hypothesis does not account for the reference of pain to regions supplied by distant segments (Theobald, 1941; Lewis, 1942; Wolff and Hardy, 1947). Finally, I find it hard to believe that such well-known phenomena as summation, inhibition and irradiation operating centrally have no part in the explanation of phenomena such as referred tenderness, which it seems to me put an

unnecessarily severe strain on the hypothesis that peripheral mechanisms alone are involved.

For this reason, I shall now discuss the theory that the phenomena of referred pain depend upon some mechanism located in the central nervous system. Fig. 2 illustrates the simplest mechanism for which there is some anatomical and physiological evidence and which I believe can also account for referred pain and the phenomena associated with it.

It assumes that a proportion of cutaneous and visceral (or deep somatic) afferent fibres each converge on to one and the same neuron in the central nervous system. In other words, I have now placed the point of convergence not only away from the periphery but in particular in a region where the principles of summation, inhibition and facilitation are applicable. Such a mechanism not only accounts for referred pain, which is approximately segmental in distribution, but if (as is usually assumed) pain ascends in the antero-lateral column of the cord, to the thalamus and thence to the "pain centre" in the brain via a chain of neurons, it can also be made to account for pain referred to distal segments. For, to explain such observations, it is logical to assume that convergence may take place on to any neuron in the course of a particular chain. In other words, that pain may be referred to the distribution of C.N. V by impulses arising from the heart (Lewis, 1942; Wolff and Hardy, 1947).

This theory reveals its most attractive aspects if one also adopts my suggestion that pain is related to the particular spatio-temporal pattern of activity which is transmitted by certain nerve fibres to the spinal cord and not to the fact that the nerves in question merely happen to be active. I can perhaps best illustrate this point by reference to experiments on tickle recently reported by Ebbecke (1957).

Briefly, he has shown that a sensation of tickle is reported when the *skin* anywhere over the body surface is suitably stimulated. Moreover, subjects find that they can evoke a sensation of tickle by stimulating themselves, provided they are given an appropriate stimulus object and told what to do. Tickle can be evoked most easily in zones of acute tactile sensibility by the application at suitable intervals of a rapid series of stimuli which, when delivered singly, are reported as very light contact. It is also of considerable interest to note that tickle evoked in this way cannot be aroused from the skin in subjects in which the antero-lateral tract in the spinal cord has been divided, although their touch sensibility may still appear to be normal.

The most convincing series of experiments, which illustrate the particular points I want to make, can be done on oneself. Take a tuning fork (of the kind used by otologists), attach a fine bristle to it, start the fork vibrating and apply the bristle anywhere on the lower lip near the junction of the skin and mucous membrane for half a second or so, at intervals of about 5 seconds. Almost at once there is an intolerable tickling sensation which persists for as long as a minute if one refrains from wiping the lip to get rid of it, for the sensation is immediately abolished if the lip is wiped. If one stimulates the lip repeatedly in this way and at the same time refrains from wiping it, both the strength of the sensation and the length of time for which it persists will increase. Moreover, adjacent areas of skin from which a single train of stimuli previously evoked no sensation of tickle will now be responsive to a single light touch stimulus. Indeed, the sensation can be made to irradiate for some distance in this way. The affected area, however, is not uniformly sensitized, the stimulated zone remains the most sensitive, while the sensitivity falls towards the margin which is indistinct. By contrast, one can also stimulate the lip with the same object in such a way as to prevent a sensation of tickle being aroused in the manner I have just described; furthermore, this inhibitory state can be made to spread in exactly the same way as the state of excitation was made to spread. All that is necessary to evoke a state of inhibition for tickle is to stimulate one's lip in exactly the same way but to reduce by 50% or more the interval of time between the application of the trains of stimuli.

Here, then, is clear-cut evidence that the pattern of activity impinging on the cord from one and the same set of endings determines the kind of sensation which is reported. There is no question here of the liberation of a chemical substance in the periphery (particularly in view of the effect of cordotomy on tickle) by stimuli evoked elsewhere in the body. Furthermore, the experiments of Rensch and Franzisket (1954) and Franzisket (1955) suggest that this mechanism (which is presumably the sensory arm of the scratch reflex) is primarily located in the spinal cord and not in the brain. It is also clear from these experiments that irradiation, excitation and inhibition have a role in the reports which are evoked when the skin is stimulated.

Thus, it seems clear that, provided in man peripheral axons from different regions such as the gut and deep tissues converge on to a neuron which also receives impulses from the skin, the phenomena of referred pain can be satisfactorily explained on the basis that the mechanism is situated in the central nervous system. The central mechanism I have suggested provides for the possibility that impulse patterns entering the spinal cord can not only be modified

at the segmental level at which they enter but also at other positions on their way to the "pain centre."

Having started with a definition of pain in my quest for the mechanism of referred pain, it seems that I have fathered theories which abhor a rigid definition of pain in terms of anatomical arrangements and physiological mechanisms. Indeed, the theories I have discussed are most acceptable when it is assumed that there will be as many pains as there are patients reporting them. Fortunately this also implies that there are almost as many and diverse ways of treating them.

The facts concerning the mechanism of referred pain and the phenomena associated with it are too few to allow of any one theory being wholly acceptable. It should, however, be possible to design experiments to put some of the suggestions which I have made to the test.

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Dr. G. Gordon (Laboratory of Physiology, Oxford):

The Physiological Basis of Referred Pain

Dr. Weddell has made my task easier by presenting clearly the two general hypotheses put forward to explain the phenomenon of referred pain—that of the branching of peripheral nerve fibres and the more traditional one of central synaptic convergence. What I must do now is to examine each of these from a physiological point of view, asking first whether each, as a hypothesis, will explain the hyperalgesia, the muscular rigidity and the actual reference of pain, and then asking whether either is supported by objective physiological evidence.

It is clear, I think, that each hypothesis can explain the facts in a purely diagrammatic sense. In each case the false reference of pain is the result of the confluence of a visceral or deep somatic path with a cutaneous path, such confluence forming an inevitable part of any hypothesis which proposes an objective basis for the phenomenon. In each case muscular rigidity is a form of reflex activity akin to the flexion reflex, readily reproduced in the spinal animal by mishandling deep somatic or visceral structures (*see* Lewis and Kellgren, 1939). Cutaneous hyperalgesia, on the peripheral hypothesis, is the result of impulses running antidromically to the skin and there setting up an excitable state which lowers the threshold of neighbouring cutaneous nerve fibres which mediate pain: on the central hypothesis it is explained by visceral impulses lowering the postsynaptic threshold at the site of convergence, so that cutaneous impulses more easily excite the secondary common pathway. It is worth noticing that, on the central convergence hypothesis, the cutaneous fibres concerned need not be "pain fibres" in the sense that pain is felt when they alone are stimulated: pain may be felt only when a deep sensory path is simultaneously active. It is a fact that the results of anæsthetizing the cutaneous area of reference have been extremely conflicting, some having abolished visceral pain in this way and some having failed to do so; but this conflict has been resolved to some extent by showing that the efficacy of cutaneous anæsthesia can depend on the strength of the visceral stimulus (Doran and Ratcliffe, 1954), and it is known moreover that on occasion pain can even be referred to phantom limbs (Cohen and Jones, 1943). These

facts can be explained on either hypothesis: in each case the effect of cutaneous anæsthesia will depend on the quantity of visceral impulses and hence their capacity to "fire" the central pain pathway on their own account without summation with cutaneous impulses.

In examining these two hypotheses in the laboratory one must remember that there is no *a priori* ground for assuming that all the curious subjective phenomena which we group under the heading of referred pain have in fact a single common physiological basis, and one must not reject out of hand a hypothesis which offers only a partial explanation. No crucial evidence exists at present which causes either hypothesis to be rejected; but some probabilities arise from the evidence. There is, in the first place, perfectly clear proof of the confluence of cutaneous pathways in the central nervous system with deep somatic and visceral pathways. Many examples of this confluence have been recorded in the last few years, the evidence usually taking the following form: an electrical record is made of the activity of a single central neurone (or of a group of neurones), and it is shown that activity in this neurone can result from stimulating either a cutaneous nerve or a deep sensory nerve. It is important to prove that it is really the same neurone which responds in either case, and this is done by showing that after the neurone has been excited from one peripheral source a period of time elapses (the "unresponsive period", a term analogous to "refractory period") during which it cannot be excited from the other peripheral source. It has been shown in this way that in the cerebral cortex and subcortical white matter of the cat interaction occurs between cutaneous and deep somatic pathways (Mountcastle *et al.*, 1952), between cutaneous and splanchnic pathways, and even between pathways from two related skin areas (*see* Amassian, 1952). It has to be emphasized, however, that this extremely interesting information is not necessarily relevant to the question of referred pain. Clearly it will always be impossible to prove that any purely objective evidence from animals does give the actual basis for referred pain; but the likelihood of the evidence being relevant will be enormously increased if one shows not only the confluence of the central connexions from the two peripheral sources, but also that this occurs in the main cerebral projection system for sensory fibres which could reasonably be expected to mediate pain in man. From now on I shall confine myself to evidence which conforms to these criteria.

Data from many sources have contributed to the view that the peripheral elements concerned in mediating pain and nociceptive reactions are particularly concentrated among the smaller myelinated and the unmyelinated fibres of sensory nerves: the former have a mean diameter of about 4μ and are responsible for the Aδ wave in the compound action potential of the nerve. I shall call them *delta* fibres. When recording the electrical responses of a central cell to stimulation of a peripheral nerve, one can control the peripheral stimulus by recording also how the nerve responds to it, so that one knows whether the *delta* fibres are being stimulated or not. Gaze and I (1954), using this technique, were able to show that in the main cutaneous relay nucleus of the thalamus (*n. ventralis postero-lateralis*) of the cat and monkey there were cells which seemed to be excited specifically by stimulating cutaneous *delta* fibres and by applying noxious stimuli to the skin. This seemed a promising situation in which to look for interaction between visceral and cutaneous paths, and this was done by my colleague McLeod (1956), using the splanchnic nerve as the source of visceral impulses. This nerve has a group of large myelinated afferent fibres, which probably do not concern us here, and also a group of *delta* afferent fibres which have been shown to be concerned in responses to noxious stimuli (Gernandt and Zotterman, 1946). McLeod found many cells in and around *n. ventralis postero-lateralis* of the thalamus which responded to stimulating one or other of these fibre-groups in the splanchnic nerve: they were mainly to be found in the part of the nucleus which receives impulses from the skin of the trunk, though some were found in the limb regions. The interesting point is that the majority of these cells responded also to stimulating the skin—usually the skin of the trunk, but sometimes that of the limbs or tail. Cells such as these were found in both the ipsilateral and contralateral thalamus.

These facts seem to me to provide us with at least a plausible experimental basis for referred pain of visceral origin. Undoubtedly one would be more convinced if it had been shown that the same systematic basis existed in the cerebral cortex also; and it is to be hoped that it will be looked for. Does the evidence now allow us to choose between the two hypotheses with which we started out? Strictly it does not, because the hypotheses do not exclude one another. There were certainly some features of these particular experiments (McLeod, 1957) which made it seem unlikely that the confluence of pathways was due to branching of peripheral fibres. If it were due to branching, it is extremely difficult to explain why the "unresponsive time" of the pathway should invariably depend on which of the peripheral fields was stimulated first, or why the response to stimulating one of the two fields should sometimes be intermittent whereas that from the other field should be regular and consistent. Only an improbably elaborate argument can reconcile these facts with the hypothesis of branching fibres. Even if these particular facts cannot be explained in this way, a few peripheral fibres may branch in the suggested manner nevertheless; and this could be investi-

gated fairly readily by seeing whether stimuli applied to visceral nerves do, in fact, cause action potentials to run antidromically in cutaneous nerves of related segments.

Whatever other factors may be concerned, then, it seems that there is a synaptic convergence mechanism present in mammals, at the thalamus or at a lower level, which is capable of explaining the reference of pain, usually to neighbouring parts of the skin surface, sometimes to more remote parts. We do not know the level at which this convergence occurs, or even whether it is confined to one level. Certainly some such convergence may occur at a spinal level, as Widén's (1955) results have shown; but it has not yet been discovered whether the interaction seen by Widén is occurring in the main spino-cerebral sensory pathway. Finally, let me say that although the experimental evidence which I have described is probably the right kind of evidence to bring to bear on this problem, the question of its actual relevance to the problem of referred pain is nevertheless pure guesswork.

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Dr. R. M. Mason (London Hospital):

I propose to speak primarily from the clinical aspect of referred pain and to limit myself to the beginning and the end of the anatomical pathways and physiological mechanisms dealt with by the two previous speakers, i.e. the effect of pain on the patient at one end and the pathology of the lesion causing the pain at the other.

Our first clinical problem is the difficulty of assessing the severity of the pain. It seems clear that even for the trained investigator the translation of sensory experience into words may be extremely difficult (Kellgren, 1949). How much more difficult is it for the average hospital out-patient, especially where the emotional component may be high, since, as Medvei (1949) pointed out, pain is "close to the centre of personality" and cannot be separated from the emotional quality of the individual. All we can really say of the character of any pain is that it is unpleasant; nor indeed does the English language contain a word to describe the effects of the relief of pain (Critchley, 1934). Epicurus apparently took the view that the absence of pain is in itself a pleasure, but as Medvei rightly said pleasure is not the correct word, and the physiological and psychological gratification following immediately on the relief from pain is perhaps regarded only by lunatics as equal to pleasure. It is all too easy for us to be misled into false estimates of the severity of the patient's pain and we have to remember that a trivial lesion can give rise to severe pain and a serious lesion, constituting a major threat to the patient's survival, may give rise to no, or to only trivial, pain. Some bone conditions are easy to miss.

Case I.—A 22-year-old salesman was referred to the Orthopædic Department of the London Hospital with a four-and-a-half-year history of obscure pain in the left leg. It was mostly situated in the adductor region of the left thigh but had extended to the left knee. He had been to another hospital where no derangement of the knee had been found and he had been reassured but the pain continued, aching in the knee, calf and ankle, intermittent but becoming more severe and eventually extending round the iliac crest and across the groin. Osteopathy failed to help. Physical signs amounted to no more than a slight wasting of the left leg but an X-ray showed an area of sclerosis just below the left lesser trochanter, containing an area of rarefaction, and within this area of rarefaction a further ring of sclerosis. This was osteoid osteoma, the cause of his pain.

This curious condition of osteoid osteoma is just the sort of pathological lesion which can give rise to referred pain, in which serious mistakes can be made in discounting the severity of the pain simply because no physical signs are found, and the pain is relieved by one aspirin.

Case II.—A 70-year-old woman was referred complaining of pain in the left knee and leg of three months' duration. Clinically there was some thickening of the lower leg. She had a sedimentation rate of 125 mm. in the first hour (Westergren) and a hæmoglobin of 65%. X-ray of the left tibia showed the characteristic appearance of syphilitic periostitis and her quantitative W.R. was positive in serum diluted at 1 in 1,600. Further skeletal survey showed similar changes in the forearm but these were quite painless illustrating the discrepancy between the severity of the pain and the pathology of the lesion.

Then, of course, there are the more frequent sources of error.

Case III.—A young woman of 36 was referred by her doctor "I think this patient has a spinal lesion with referred pain in the right calf. It is now preventing sleep and I would be grateful for your advice and treatment". This had developed three months previously with pain in the right calf on getting out of bed. Her doctor had examined her at that time and found tenderness in the calf and thought she had a muscle strain. She had recovered but two months later had returned with an "uncomfortable feeling" in the back of both thighs worse in bed at night. This had been ascribed to sitting on a hard chair at work—she was a medical secretary—but by the time I saw her she had limited straight leg raising and limitation of spinal flexion with a scoliosis. X-ray of her spine showed secondary deposits in L.3 and 4 and further skeletal survey showed multiple bone deposits. On re-examination there was a firm tumour in the upper medial quadrant of the left breast with enlarged axillary glands. Biopsy showed this to be an adenocarcinoma and a bilateral oophorectomy and adrenalectomy was carried out. Post-operative X-rays showed rapid resolution of the secondaries and she completely lost her pain. The basic pathology of the lesion was unchanged and the loss of pain does not alter the ultimate prognosis.

The next patient illustrates the other common mistake.

Case IV.—A 59-year-old butcher was referred to Medical Out-patients complaining of substernal pain with a diagnosis of ? angina. He was there noted to have a dorsal kyphosis but ECG was normal. X-ray of the dorsal spine was interpreted as showing osteo-arthritis and he was therefore referred to the Physical Medicine Department. We took the precaution of taking a better quality X-ray, however, and this now showed collapse of the dorsal vertebræ. Sedimentation rate was 140 mm. in the first hour (Westergren), hæmoglobin 64% with abnormal plasma proteins. Marrow biopsy showed large numbers of plasma cells characteristic of myelomatosis.

On the other side of the coin there is the occasional patient who presents with what should be a painful condition but without pain.

A congenital indifference to pain is recognized as occurring in children giving rise to a characteristic picture of a severe arthritis of the ankles and tarsus (Murray, 1957). In these children fractures may only attract attention because of the resulting deformity and osteomyelitis is a common complication.

Case V.—A 58-year-old decorator was seen recently complaining of weakness of the limbs for twelve months. His main complaint was of loss of strength of his arms and loss of grip, making it difficult for him to work. He did agree that his joints had become swollen but he had not been off work at all. X-rays showed severe rheumatoid changes. His central nervous system was completely normal except for loss of pain sensation.

I think that this problem of assessing pain with these varying factors is a most important one. Measurement of pain thresholds is difficult and at least 82 methods have been devised (Goetz *et al.*, 1943), these being mechanical, electrical, chemical and thermal which suggests that none of them are really satisfactory. Perhaps the simplest is that described by Libman (1934) who found that pressure in the direction of the styloid process is painful in some individuals and not in others. He classified people into three groups—hypersensitive, normosensitive and hyposensitive—on their response to this test. Keele (1954) reintroduced the pressure algometer which had been used in the last century for assessing analgesia in tabetics. Whatever method is used it is necessary to distinguish clearly what is being measured, distinguishing, that is to say, the point at which pain is felt—the pain perception threshold—from the pain reaction threshold, what I would call the "Ow!" point, and the point at which the pain becomes intolerable which is the maximum pain tolerance. I suspect that many of our patients have low "Ow!" points, even if their pain perception thresholds are normal. So far as I know we have no data on this. Keele has provided us with data on normal controls in which he has shown that the pain perception threshold by his criteria is distributed as follows—23% were hypersensitive and 15% were hyposensitive. I think a similar study on the out-patients in one of our departments would be of great interest. It seems to me that unless we can tell to which group the patient belongs when we are trying to assess his symptoms we must be in difficulties in determining the amount of pain, quite apart from any anatomical considerations. There are, however, many difficulties such as the variations produced by changes in the skin temperature to which Beatty and Woodmenay recently drew attention (1955).

We have to remember that pain whether referred or not may become "an old friend". Tic douloureux lends itself particularly to a study of the effects of relieving pain, for the pain is severe and complete anatomical block of the sensory root of the trigeminal nerve is possible. Penman (1954) found that some 22% of his patients showed subsequent neurotic symptoms after such relief. As he says the transformation from a patient in frequent severe pain but not weeping, to one out of pain but weeping, could not by any feat of reasoning be called improvement. How often does that not apply in lesser degree to our patients. I can well recall one whose chronic backache referred from multiple disc degeneration was relieved by a month of strict bed rest, and of having had the foresight to warn the general practitioner that I hoped we would not altogether cure the patient for I anticipated disaster if we did. Shortly after her return home cured of her backache, she had to be readmitted in agitated depression and required electric convulsant therapy.

Even where a careful history and physical examination will give us the anatomical site of the lesion giving rise to referred pain, it is of even greater importance to us clinicians to identify the pathology. I have already mentioned two or three cases of this kind but the pathological nature of the lesion gives rise to some unexpected surprises. I think one can learn from these experiences and that they bear repetition.

Case VI.—An Assistant Matron of 24 came up to Out-patients recently complaining of attacks of acute low backache and left sciatic pain, the first attack having been at the age of 17, putting her to bed for three weeks. She still complained of occasional bouts of pain down the left leg. Initial examination revealed no physical signs. An X-ray showed bilateral sacro-iliitis.

Case VII.—Another surprise was a male Indian of 34 years who was referred by his doctor for advice on the treatment of his low backache after a radiological diagnosis of ankylosing spondylitis had been made. He gave a six years' history quite characteristic of ankylosing spondylitis, of morning stiffness in the low back relieved by getting about, and there was occasional stiffness in the groins and the neck. Examination revealed a moderately limited lumbar spine. His chest expansion was 1½ in. The X-rays showed a diagnostic picture of ochronosis of the spine with frayed thinned disc spaces and his urine contained large amounts of homogentisic acid.

These two cases represent fairly simple surprises. I would like to describe two more rather more complex problems of referred pain.

Case VIII.—A motor cycle agent of 46 was referred to Mr. H. Osmond-Clarke with a three years' history of vague lumbar and sciatic pain on the right side after he had lifted a motor cycle. He had not responded to plaster jacket, &c., and when seen by Mr. Osmond-Clarke was also complaining bitterly of pain in the right knee. No abnormality could be found in this joint and it was considered that it was a referred pain from the low back. X-ray of the spine showed definite forward slip of L.5 on S.1 and the oblique view showed quite clearly a defect in the pars inter-articularis. When he came into hospital he developed a considerable effusion into the knee-joint and when I saw him his sedimentation rate was 43 mm. in one hour (Westergren). X-ray of the right knee showed subchondral cystic changes in the patella with a patchy osteoporosis which was attributed (wrongly) to osteo-arthritis. He went rapidly downhill and after various complications, interpreted as embolic phenomena in the lungs, he developed symptoms of a severe transverse cord lesion in the lower cervical and upper dorsal region and died. Post-mortem revealed diffuse carcinomatosis with a primary carcinoma of the lower lobe of the left lung. He did have a spondylolisthesis of L.5 on S.1 but the bodies of both vertebræ were infiltrated by growth of osteolytic deposits, and there was "considerable erosion and partial destruction of the right patella, the central portion of its articular surface being replaced by soft greyish growth". Nearly every other tissue of the body was also infiltrated with secondary carcinoma.

Case IX.—A man of 32 with a diagnosis of Tietze's syndrome. He complained of pain in the region of the right trapezius and in the low back with a dull aching pain in the left loin, and of a tender swelling over the left third costal cartilage. His history was that he had cut his left thumb some three years previously whilst working in a slaughter house and the healing of this wound had been delayed for about a year. Six months after the injury he had developed a sharp pain in the left side of the chest and shortly afterwards this swelling had appeared. It had given rise to a constant dull aching pain. Later he had developed pain in the right shoulder region and left loin and had been readmitted to hospital where full investigations had failed to reveal any significant findings. He had continued to lose weight—about 4 st.—and was obviously in pain. On examination, apart from a tender hard swelling over the costochondral junction of the left third rib, he was very tender over the third and twelfth dorsal vertebræ and all his spinal movements were much limited. The only positive pathological or radiological finding was a little collapse of D.12. A further biopsy was carried out by Mr. Vernon Thompson revealing a secondary carcinoma consisting of trabeculated polygonal squamoid cells with a few giant cells. He was treated with radiotherapy with some symptomatic improvement but subsequently died. Post-mortem showed a small white tumour in the left kidney, ¼ in. in diameter, which proved to be a hypernephroma, and secondary deposits were found in the third and twelfth dorsal vertebræ as well as in the third left rib and elsewhere.

Conclusion

I have tried from these examples to show the clinical application of the basic sciences of anatomy and physiology which have to be coupled with pathology, and are sometimes complicated by psychiatry, to make up the complex problems of referred pain which form our daily lot.

I am grateful to Mr. H. Osmond-Clarke for permission to publish Cases I and VIII.

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Section of the History of Medicine

President—DOUGLAS GUTHRIE, M.D., F.R.C.S.Ed., F.R.S.Ed.

[*May* 1, 1957]

The Pattern of Australian Medical History

By BRYAN GANDEVIA, M.D., M.R.A.C.P.

Wunderly Travelling Scholar in Diseases of the Chest, Royal Australasian College of Physicians

"... the writer (of a history of medicine) may be tempted to exaggerate the importance of great discoveries and to lay great stress on the lives of famous men. It should be remembered that this is only one aspect of history, a survey of the peaks and not of the valleys, a study of the milestones rather than of the miles between."—DOUGLAS GUTHRIE, *Int. Rec. Med.*, 1956, **169**, 700.

The history of medicine in Australia is a small valley in the vast realm of medical history, but in some respects it is a fertile one.

The introduction of new concepts and techniques amply repays careful study in Australia. I shall draw attention to some of our medical pioneers, in the forefront of whom are those with the courage and initiative to try new ideas, whether original or not, and those whose foresight and planning contributed to subsequent development. In Australia the first penal settlements had their own peculiar problems; the factor of distance led to the development of the "flying doctor" service and significantly influenced the character of general practice.

The basic pattern of Australian medical history is readily defined. There was first an era of exploration, before settlement, limited to the coastline, and with this may be classified, from the medical viewpoint, many of the subsequent voyages and expeditions of exploration in the half-century or more after the first settlement. Secondly, there was the early colonial era (1788–*c.* 1850), which includes the penal era and a short ensuing period of economic and legislative dependence upon the United Kingdom, somewhat euphemistically termed the romantic era. Thirdly, there was the late colonial era, extending from about 1850 to the turn of the century. The special significance of this period lies in the fact that it coincides not only with the advent of modern scientific medicine but also with the achievement of independence by the several colonies and with the social consequences of increasing population and prosperity and in particular of the discovery of gold. The fourth era, of clinical science, in which we now live, is as yet young in Australia. The only reference which I wish to make to it is to observe that the modern development of Australian medicine as a national enterprise, based largely upon graduates of her own universities, is due chiefly to a small group of doctors of the latter part of the nineteenth century. Most of them were emigrants from Great Britain, and in them our countries may jointly take considerable pride.

THE ERA OF EXPLORATION

It was not until the seventeenth century that visitors to Australia were in any sense numerous. One must be mentioned because he was the first medical man known to have set foot on our shores. In 1629 the *Batavia*, commanded by Francis Pelsart, was wrecked off the coast of Western Australia. About 180 people landed on a near-by island. Pelsart sailed 400 miles up the inhospitable coast in the ship's boat looking for water. Finding none, he simply went on to Batavia and came back with a rescue ship. Meanwhile, the apothecary or surgeon aboard the wrecked ship, Jerome Cornelis, who had in any case planned to mutiny and forsake medicine for piracy, had taken the liberty of murdering most of the survivors, except for a few women. On the return of Pelsart, in unexpected strength, Cornelis had his hand chopped off and was then hanged. So much for tradition.

The most notable voyage of exploration connected with Australia was that of Captain James Cook (1768–71). At the request of the Royal Society, the voyage was undertaken to observe the transit of Venus from Tahiti, after which Cook was to investigate New

Zealand and to seek confirmation of the existence of a great Southern Continent. All this Cook did, and in particular he mapped the east coast of Australia. The scientific side of the expedition, under the personal direction of Sir Joseph Banks, was also an outstanding success. The medical interest of this voyage lay in the striking freedom of the *Endeavour*'s company from serious illness of any kind, and from scurvy in particular, prior to the arrival of the ship at Batavia late in 1770. Banks wrote proudly in his journal that "our people . . . might truly be called rosy and plump. For we had not a sick man among us." Indeed, this was the first trans-Pacific voyage to be completed without the development of serious scurvy. Captain Cook himself has usually been given sole credit for this, notably because of the cunning ruse which he adopted in order to entice his crew to eat sauerkraut: he allowed the men to see that the officers ate it daily but he left it optional for them—within a short time he had to ration it all round. Cook is known to have taken great care in the selection of his crew, and some of the credit may be due to his two surgeons, Monkhouse and Perry. The Admiralty, which took no official notice of Lind's work until 1796, sent detailed orders to use malt wort, together with two books on this subject by a Dr. MacBride. Perhaps more important, Dr. John Fothergill, the Quaker physician, sent concentrated orange and lemon juice to Joseph Banks, and this was accompanied by a long letter of instructions from Dr. Nathaniel Hulme, an influential naval surgeon and a foundation member of the Medical Society of London. Finally, some credit may be due to Dr. Carl Solander, who was a member of Banks' entourage. Whoever or whatever was responsible, Cook's voyage was a remarkable feat; scurvy remained a major problem on the Australian run well into the nineteenth century, and was recorded as late as 1867.

The Early Colonial Era

We may now consider the conditions of convict transportation, with special reference to the first three fleets to arrive at Sydney Cove, Port Jackson. The first, under Arthur Phillip, arrived in January 1788, and consisted of eleven ships bearing over a thousand souls. Only 45 of 756 (6%) convicts died on the seven months' voyage, and 3 of the remaining other personnel (the difference is statistically significant); Phillip was a good commander and he was ably supported by his senior surgeon, John White (1750–1832). White's "Journal of a Voyage to New South Wales" (1790) is the starting point of Australian medical literature. Many of the prisoners were carriers of disease, if not actually ill, at embarkation. The mortality was probably no more than could be expected in view of the overcrowding (which existed on board long before the ships sailed), and the inevitable restrictions on food, fresh air and exercise. The second fleet arrived in June 1790. Of approximately 1,800 prisoners, rather less than a third died *en route*, and almost as many again were put ashore sick and dying. The Rev. Johnson described their arrival: ". . . great numbers were not able to walk, nor to move hand or foot; such were slung on the ship's side in the same manner as they would sling a cask. . . . Upon their being brought up to the open air some fainted, some died upon the deck, and others on the boat before they reached the shore. When come on shore many were not able to walk, to stand, or to stir themselves in the least . . . . Some creeped upon their hands and knees, and some were carried upon the backs of others." In the crowded conditions the prisoners had found it easy enough to conceal corpses, until the stench gave them away, in order to gain the deceased person's share of the rations. Dysentery, scurvy and probably typhus and typhoid fevers were the specific diseases responsible. However, the tragedy of the second fleet lay not only in its own pitiable state but also in the inability of the original settlement to succour them. For months it had been on the brink of starvation itself, for it was far from self-supporting. The chief factors contributing to this were the lack of experienced farmers, the failure of the crops and gardens, and the death or loss of much of the livestock. The strain on the tiny hospital had been great throughout; on its arrival £1,400 worth of surgical equipment and supplies, found to be of inferior quality, had to be thrown away. The sudden influx of 500 patients was a calamity to the settlement; perhaps the major factor in its survival was the dogged, determined leadership of the ailing Governor Phillip. In the third fleet, which arrived in 1791, the mortality was down to about 10%, but a month after its arrival Phillip reported that nearly 600 convicts were under medical care and constituted a "deadweight on the stores".

Having described these conditions, it is necessary to refer briefly to the measures taken to ameliorate them. It must be remembered that in the years which followed the first settlement England was beset with the economic and military problems associated with the Napoleonic wars, and that even granted every facility medical science was not yet ready to cope with the problems involved in the mass transportation of a convict population. In 1800, among other changes, the £23 per convict, dead or alive, paid to the transportation contractors, was replaced by £18 per head, with a bonus of £4 10s. 6d. for each one safely landed. Despite some improvements, mortality and morbidity remained high until the

adoption of recommendations made in a report, described as a model of its kind, prepared by William Redfern, a colonial surgeon and ex-convict, in 1815. Redfern's advice regarding fresh air, diet, personal cleanliness and clothing is obvious to-day. He advocated the appointment to the transports of naval surgeons; previously these appointments had been made by the shipowners, and the appointees were usually "students", derelicts or failures. Subsequently surgeons-superintendent were appointed and given wide powers. Over the years their responsibilities grew, and ultimately we find them responsible even for the religious and general education of the convicts on the voyage. Later, they were employed as immigrant agents, recruiting immigrants in England and travelling out in medical charge of the ships which brought them; somewhat modified, this service continued through most of the nineteenth century, long after the transportation of convicts had ceased.

The health of the tiny settlement, perched precariously on the edge of a vast continent, during what have been called the "hungry years", was much as might be imagined. Injuries, snakebite and sunstroke were common, but the major problems were dysentery, typhus and typhoid fevers, tetanus and venereal diseases, aided and abetted by scurvy and malnutrition. For over two years there was no fresh meat, butter or milk, and only very little in the way of vegetables. White and Considen, one of the assistant surgeons, found that the native sarsparilla was a valuable antiscorbutic agent, that the gum of the native myrtle was astringent and that eucalyptus oil had useful properties. Of venereal disease, Governor Phillip wrote in 1789 " . . . it has gained such a footing in the Settlement that I now doubt if it will ever be done away with. The Precautions I ordered to be taken in England have been rendered ineffectual by the infamous conduct of some of the Magistrates, in sending on board the transports those who have [*sic*] been turned out of the Hospitals as incurable". The first legal order relating to public health, promulgated in 1795, was one to prevent contamination by pig ordure of the stream from which the colony drew its water supply; curiously enough, we have no knowledge of the means of disposal of human excreta. The acute infectious diseases made inroads upon the relatively "non-immune" population from time to time. Trachoma was described in 1794. In the subsequent history of Australia it was always to appear on the advancing edge of civilization, disappearing as civilized living became established. Its wide distribution and curious behaviour seem to exclude causation simply by dust, heat or bacteria, and a nutritional basis has been postulated. By 1803 the colony could be described as "very healthy"; a decade earlier (1792) the mortality had been over 10% of about 3,400 inhabitants, but it had then fallen to about 2% per annum. About this time government-sponsored free settlers began to arrive; by the second decade of the nineteenth century settlers were arriving with capital, and these emigrants must have influenced the social and hygienic standard of the community for the better. By this time the degenerative diseases were beginning to replace the enteric diseases and syphilis as causes of morbidity and mortality; so too was alcoholism.

An epidemic of very severe smallpox decimated the native population in 1789, but spared the entire European colony, with one exception. The disease had not previously been established on the Continent, as far as is known; it has been suggested that the infection was introduced by Malay or Macassar fishermen, and that the colonists were immune. Variolous matter brought out with the first fleet, a conceivable source, was not apparently responsible. Vaccination was introduced by surgeons Savage and Jamison in 1804, and this led to the first signed medical paper to be published in Australia. Entitled "General Observations on the Smallpox", it was published by Jamison in the *Sydney Gazette* of October 14, and drew attention to the new "infallible preventative". Calf lymph was not manufactured in Australia until 1881.

The medical officers who ministered to the community during its early years provide a fascinating study. Their social background varied widely and their professional skill was no doubt equally variable. They were deeply involved in the scandalous traffic in rum, which largely took the place of currency, and in which the officers of the New South Wales Corps established a vicious but profitable monopoly; some of them were directly concerned in the successful plot to depose Governor Bligh, of *Bounty* fame; two of them fought a duel after a dinner party at the Governor's house. It would be unwise to judge this behaviour by modern ethical standards, just as it would be unfair to judge their professional skill by the vital statistics of the colony in the hard cold light of modern medical knowledge. They were overworked, underpaid, and administered in a clumsy and frustrating fashion which predisposed to conflict. One of the more interesting and important surgeons was William Redfern (1778–1833), whose excellent report on convict transportation we have already mentioned. Redfern was 19 and had recently passed the examination of the London Company of Surgeons when he was sentenced to death for offering advice and encouragement to the mutineers at the Nore (1797). Because of his youth, the sentence was commuted to one of life imprisonment, and he was transported

to Australia in 1801. After a year's work as assistant surgeon at the subsidiary settlement at Norfolk Island he was granted a free pardon by Governor King. By 1808, when he went to Sydney, he owned both land and houses there. Unable to produce documentary evidence of his qualification, he passed an examination set by a specially constituted board of examiners, and thus became the first person to hold an Australian medical diploma. On this board he was later to serve himself. Redfern's worth seems to have been immediately recognized. He is said to have attended the family of Governor Bligh, then a prisoner in his own house, and certainly he rapidly became a personal friend of Bligh's successor, Macquarie, to whom he was physician for many years. About this time Macquarie invited tenders for a new hospital, to be built on the grand scale which characterized public buildings during Macquarie's term of office. The result was the famous "Rum Hospital", opened in 1816, later to become the Sydney Hospital. The contractors received a virtual monopoly on the importation and distribution of 60,000 gallons of rum over several years, together with the labour of some bullocks and convicts. For a governor who had been sent out with the express orders to quell the rum traffic, it was a fantastic contract to have signed, especially without prior reference to England. Another curious feature was that one of the three contractors was the Principal Surgeon, an Irishman of uncertain medical qualifications, once allegedly implicated in some highway robbery, who may have been added to the original two contractors to give the firm financial stability. When the hospital was built Dr. Arnold recorded that "it perhaps might make a good barrack but certainly must be a very bad hospital . . . a preposterous building". Arnold doubtless kept his view from Mrs. Macquarie, who may well have been responsible for its design. Occupying a fine site in Macquarie Street, the buildings are still in use, only part of them at present forming the hospital. As an assistant surgeon in the colonial medical service, Redfern was the first medical officer to the hospital, where he worked conscientiously and well every morning. He was assisted by his apprentice, William Cowper (1800–?1855), the first student of clinical medicine in Australia, the first Australian to become a Member of the Royal College of Surgeons, and the first surgeon to the Moreton Bay (Queensland) Settlement, where he was concerned with the foundation of the Brisbane Hospital. Redfern's private practice grew to be the largest in the colony, and his work must have been of a high standard. In 1818, Macquarie recommended him for the vacant post of Principal Surgeon, "being a man of very eminent talents and an excellent scholar and possessing universal knowledge". This promotion of an ex-convict was too much, however, and Redfern's claim was overlooked. He resigned, and after some years of private practice devoted himself solely to his extensive agricultural interests. The recognition of Redfern's ability, his championship of the emancipist cause in later years, his philanthropic and social activities, his personal friendship with the Governor, all reflect a significant change in the colony over the first two decades of its existence, namely, the commencing evolution of a free, progressive settlement from the original purely penal establishment. With Redfern must be linked William Bland, another emancipist surgeon, and an even more prominent figure in political, philanthropic and educational spheres. He is also remembered as the first surgeon in Australia to ligate the innominate artery for aneurysm (1832), his case report being the seventh in the world literature. Had nearly a gallon of blood not been taken from the patient during the post-operative days there is a possibility that this might have been the first successful case.

Lest at this stage we grow too optimistic about the progress of the colony, I would quote the views of John White, written as the first Principal Surgeon was becoming embittered by the hardships and heartbreak of the early days: " . . . a country and a place so forbidden and so hateful as to only merit excretions and curses; for it has been a source of expense to the country and of evil and misfortune to us . . . there is not a single article in the whole country that can prove the smallest use or advantage to the mother country or the commercial world."

The Late Colonial Era

Unlike Sydney or Hobart, Port Phillip, or Melbourne as it became, was formed as a free and voluntary settlement in 1835; as part of Victoria, it became a separate colony, independent of New South Wales, in 1850. Almost immediately its population was swollen by the gold rush migration, rising from 100,000 to over half a million in eight years. During the 1880s there was a further influx of relatively young adult emigrants. Victoria has been chosen to illustrate the pattern of Australian medical history over the latter half of the nineteenth century partly because of these well-defined social influences, and partly because it is well-documented. The continuous publication, since 1855, of a regular medical journal, a direct ancestor of the present *Medical Journal of Australia*, and the existence of the minutes of medical societies in almost unbroken succession since 1847 have provided an invaluable basis for historical study, without compare in other states.

The epidemiology of the period is of considerable interest. Healthy young adults looking

for gold, camping without sanitation in small areas, provided ideal conditions for the spread of enteric diseases. From 1854 to 1861 typhoid fever was extremely common. From 1861, when conditions became more settled, until about 1890 it remained a common disease, but thereafter its prevalence decreased. Acute progressive tuberculosis in young adults decreased after 1861, prior to which it had been a major cause of mortality. About fifteen years later the mortality rate from the same type of disease in "non-immune" young adults rose again; these were in large part the children of the period 1850–1865, which was not unnaturally associated with a high birth rate. Towards the turn of the century, the age distribution of fatal cases assumed a more usual form. Incidentally, the practice of sending consumptives to Australia to take the cure had long been well established, and indeed among the survivors of this arduous treatment were some noted medical practitioners.

Another sequel of the increased birth-rate of the gold rush period was a high mortality from acute infectious diseases in children in the subsequent decade (1861–1871); in fact, whole families were lost in this way. Diphtheria burst upon Melbourne in 1858, the year in which it first assumed epidemic proportions in England; it is remarkable that by the time the third, if not the first, case appeared in Melbourne the disease was correctly diagnosed and distinguished from non-diphtheritic croup. The third patient, the child of Mrs. Dewar, has the distinction of undergoing the first tracheotomy for this condition in Australia. It was performed by Edward Barker (1818–1885), former dresser to Liston at University College Hospital and later first lecturer in surgery at Melbourne University, and James Rudall. It was unsuccessful, but Rudall later performed the first successful tracheotomy for diphtheria in 1865—an interesting reflection on the relative importance of toxæmia and respiratory obstruction. After the world-wide epidemic of 1858, Victorian epidemics of diphtheria were unrelated to epidemics in England. Measles appears to have behaved differently, for in this case fluctuations in English mortality rates tend to be reflected in the Victorian figures, suggesting that the disease may have been successively reimported. There were several sharp epidemics with high fatality rates prior to 1900, when transition to an endemic disease was shown by a more or less constant death-rate a little above that of the interepidemic periods of the previous era. A similar phenomenon occurred with whooping cough. Scarlet fever, with malignant sore throat, occurred in several vicious epidemics, but, as overseas, its severity declined about the turn of the century.

It is apparent that for all these conditions the period 1890–1900 was a critical one; several factors were involved in the changes which took place. One was the approaching stability of the age constitution of the population with the elimination of large groups of susceptible individuals. A second was the introduction of sanitation and improved water supply. Public interest in hygiene was fostered in Victoria by a violent controversy on the role of contagion in the ætiology and spread of all these conditions, as opposed to their propagation by effluvia from cesspools and the like. Erysipelas and wound infection—"hospitalism"—were so common at the Melbourne Hospital that casualties feared nothing so much as going there. These and other matters received much local publicity, and indeed it was the useful age of lay "medical journalism" the world over. Politicians and others were also conscious of the passage of the Public Health Act 1875 in this country. It is gratifying, although in the circumstances not surprising, that a Royal Commission on Sanitary Reform was set up in Melbourne at this important time; its valuable report was largely the work of Sir Harry Allen.

William Thomson (1820–1883), from the Andersonian School of Medicine in Glasgow, was in the forefront of the battle for the contagionists. He published sound work on typhoid fever, but his most interesting books—he was a prolific author—deal with tuberculosis. He inveighed against the practice of sending consumptives to Australia, not only because this had no influence on the course of the condition, but also because these people served as a source of germs, spread as dried sputum particles, which were the cause of the disease. He supported his contentions mainly by careful epidemiological studies, but in 1876 he published a notable book "The Histochemistry and Pathogeny of Tubercle", in which he analysed the pathology and histology of pulmonary and intestinal tuberculosis, reviewed current knowledge of biochemistry and bacteriology, and concluded that the disease was due to a living micro-organism. He clearly affirmed the principle of chemotherapy when he looked forward to a "(chemical) means of killing parasitic particles in living tissue without at the same time destroying its own integrity". I am sorry to say that he regarded Koch, who identified the tubercle bacillus seven years later, not as the great man who had brilliantly confirmed his views, but rather as one who had merely done what he was told, and that without acknowledgment. He was an interesting personality; he wrote a book which showed that Bacon wrote Shakespeare, and he wrote "blackguards" across a notice, still preserved, from the Medical Society of Victoria, and returned it. The incident indicates why his more elaborate literary compositions failed to meet with the reception which they undoubtedly deserved even in his own country.

A more influential man in his day was J. T. Rudall, F.R.C.S. (1828–1907), who has already been mentioned in connexion with tracheotomy. Rudall went to Melbourne in 1858, having graduated from St. Thomas's Hospital, and having spent some time on an expedition in search of Sir John Franklin. He was a competent pathologist and microscopist; he prepared a section of the diphtheritic membrane from Mrs. Dewar's child and showed it to the Chief Justice, among others. He is best known as "the father of Australian ophthalmology", a title to which his numerous publications, his operative skill in this field, and the fact that he was the first person known to have used the ophthalmoscope in Australia, all give justification. He was also the first in Australia to perform amputation through the hip-joint (1868), and the first to do the operation of gastrostomy (1867), assisted on this occasion by W. C. Rees, one of the first Melbourne graduates. Prior to the latter operation, he passed an œsophageal bougie in an attempt to overcome the obstruction, and he examined the material on the end of the bougie for cancer cells. This must be a very early attempt at diagnosis by means of "exfoliative cytology". Incidentally, the result was a "false negative". His sound consistent work, which included much for medical organizations and public hospitals, spans almost the whole half-century which we are considering, and he may well be chosen to epitomize the progress in surgical practice in Australia over this period. He is notable also for his restraint in controversy in a medical community where this quality was not always to the fore, and where, as Osler remarked "differences and dissensions seem lamentably common".

Earlier, reference was made to the men who made it possible for Australian medicine to stand "upon its own feet" at a comparatively early stage of national development. Two of these men must serve as representative of a much larger group. Seven years after the establishment of a University, little more than a decade after Victoria became independent of New South Wales, the Melbourne medical school began its work. The project was undertaken at a time of comparative economic depression after the surface and alluvial gold had been exhausted and before more extensive mining operations were producing any profits. Ambitious and courageous from the start, it rejected the advice of James Paget for a three or four year course, and adopted one of almost unheard of length—five years. On the advice of Richard Owen and James Paget, the first professor of anatomy and of physiology and pathology to be appointed was G. B. Halford (1824–1910), formerly of St. George's and Westminster Hospitals, and then lecturer on anatomy in the Grosvenor Place School of Medicine in London, where we also find Benjamin Ward Richardson and Spencer Wells. Halford, among other qualifications, was an outstanding experimental physiologist, and his monograph "The Action and Sounds of the Heart" (1860, when Halford was 36) was an outstanding contribution to experimental cardiology. With this work he became the first man to apply comparative zoological studies to the elucidation of the relationships between function and structure in man. His fascinating and scholarly Inaugural Address (1863) seems to have been written in blank verse, such was the visionary grandeur of his prose—and indeed it well might have been, for he left his audience with a famous quotation from Henry's speech to the English Army on the field of Agincourt. He at least played his part in ensuring that men should "stand a tip-toe" when that day was named. In Melbourne the influence of his teacher led him to support Owen in his battle with Huxley, in which controversy he was most violently opposed by William Thomson. He also erred in some of his contentions in regard to the pathology and treatment of snakebite, but these observations do not detract from his outstanding work in the formative years of the first Australian medical school. How easy it would have been, in a small, remote colony, more rudely practical than cultural or academic in its outlook, to have permitted a lowering of standards and a tradition of easy degrees, such as existed at that time in many famous centres. From such a catastrophe it might have taken decades to recover.

In 1882, a second great man, H. B. Allen (1854–1926), destined to render even greater service to Australian medicine, was appointed to the new chair of anatomy and pathology, Halford retaining the chair of Physiology. Allen was in every sense an Australian for he was born in Geelong (Victoria) and educated at Melbourne Grammar School. He graduated in medicine at Melbourne University in 1876 at the age of 22. It is difficult to summarize the career of a man with such wide interests and activities and such an immense capacity for work. His contribution to questions of public health and hygiene were vital in the closing years of the nineteenth century; his pathological studies on syphilis evoked world-wide interest; his editorship of the *Australian Medical Journal* for a time, his successful efforts to unite the two factions of the profession at one time represented by the Medical Society of Victoria and the Victorian Branch of the British Medical Association, and his work for a host of congresses and committees testify to his interest in medicine and the medical profession as a whole. Although universally acknowledged a great teacher and the personal creator of a great museum of pathology, he will be remembered most for what can only be described, quite inadequately, as his administrative work for the University and the medical

school. It is only to be regretted that after this auspicious beginning, Australia's first medical school had to wait almost a century before it had chairs in medicine and surgery. Australian medicine was amazingly fortunate to have Allen in Melbourne, Edward Stirling and Archibald Watson in Adelaide, and in Sydney T. P. Anderson Stuart, with his Edinburgh colleagues R. Scot Skirving and Alexander MacCormick, and also J. T. Wilson (later professor of anatomy at Cambridge).

In illustrating the pattern of Australian medical history by reference to the medical conditions of one penal settlement and to public health and medical education in a voluntary settlement much of importance has had to be omitted. In particular, little has been said of Australian contributions to medicine, and of the Australian reactions to new ideas abroad. The random observations which follow are intended to provide a little balance in these respects. Anæsthesia was rapidly introduced, despite a hostile reception in the medical press. W. R. Pugh, a Launceston surgeon, administered ether in 1847, and was closely followed in Sydney by C. Nathan and J. Belisario, and in Melbourne by D. J. Thomas. Thomas read one of the first scientific papers to be presented in Victoria to the recently formed Port Phillip Medical Association, and the manuscript of this is still extant ("On the Inhalation of the Vapour of Æther, with Cases"). Within a few months of the publication of Lister's epoch-making work, William Gillbee, an Edinburgh student, reported from the Melbourne Hospital a series of cases of abscess and compound fracture which clearly demonstrated the value of the new method. The Minutes of the Medical Society of Victoria record that the paper was "very instructive", but none the less it was to be some years before "Listerism" became generally accepted in Melbourne. Richard Tracy, one of the founders of the Women's Hospital (1856) in Melbourne, working from written instructions furnished by Spencer Wells, similarly obtained excellent results with the early cases of ovariotomy in Victoria; the first Australian ovariotomy was performed in 1852. J. H. Webb accurately described the point of maximum tenderness in appendicitis in 1884, five years before McBurney; he also advocated laparotomy for this condition, but the first Australian appendicectomy was apparently not done until 1893. The publications of J. Davies Thomas on hydatid disease, presented in book form in 1884, "remained as classics in English" until the monograph of H. R. Dew (1928). Davies Thomas is also memorable for his assertion, supported by statistical evidence, that ether was a safer anæsthetic than chloroform, but it was about thirty years before the contrary findings of the Hyderabad Commission were refuted for good by E. H. Embley's exhaustive researches on the pharmacology of the two agents. This work was done at Melbourne University, and Embley, with C. J., later Sir Charles, Martin, was responsible for the development of the heart-lung preparation which was later employed so successfully by Starling and by Anrep. Other outstanding observations up to the early years of the twentieth century were Joseph Bancroft's discovery of the parent worm of filariasis and J. A. Thompson's fundamental studies of the epidemiology of plague during the Sydney epidemic of 1900.

Finally, it remains to mention the outstanding contributions made by medical men in Australia in two fields, politics locally, and natural history internationally. As they were among the best educated people in the colonies, and as they probably outnumbered the lawyers and parsons, it is perhaps not surprising that doctors should appear so frequently playing leading roles in community life. Among them were James Palmer, editor of Hunter's works, and W. L. Crowther, Premiers of Victoria and Tasmania respectively during the formative years, but there were many others. Of the doctors' achievements in the field of natural history, where they were presented with a virgin field, suffice it to say that the breadth of their knowledge is rather awe-inspiring to a graduate of modern times.

The Study of Medical History in Australia

We may conclude by referring briefly to the study of medical history in Australia. One of the first historical papers was an admirable survey of the history of surgery by Edward Barker in his Inaugural Address as Lecturer in Surgery at the University of Melbourne. The first paper on the history of Australian medicine, by G. T. Hankins, appeared in 1891. I have recently found it possible to list about 500 papers published since that date which are relevant to this theme, and in this remarkable achievement no small credit is due to the generous policy of the *Medical Journal of Australia*, edited by Dr. Mervyn Archdall, which has published the bulk of this material. I am aware of only one society concerned solely with medical history (Section of the History of Medicine, Victorian Branch of the British Medical Association, reformed at the time of Dr. Douglas Guthrie's visit to Australia four years ago). There is a Readership and a Lectureship in Melbourne and Sydney Universities respectively. A most pressing need is for the development of a museum of medical history which covers the period coincident with our national history. A start

has been made within the Victorian Branch of the British Medical Association but progress will be slow. A second need is for manuscript material relating to Australian medicine, and I would be very grateful to learn of the existence of any relevant diaries or letters in this country so that they may be listed in the museum's files.

ACKNOWLEDGMENT

Almost all of this paper is based upon the work of others and I wish to acknowledge this debt. In the particular circumstances of this address I have chosen to give a classified list of references rather than intersperse them throughout the text; the list is not to be regarded as a selected bibliography, since it contains only papers consulted in the preparation of this review.

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Section of Proctology

President—RONALD W. RAVEN, O.B.E., T.D., F.R.C.S.

[*March* 12, 1957]

History of Excision of the Rectum [*Abridged*]

By R. P. WARREN, F.R.C.S.

I PROPOSE to outline the history of excision of the rectum for cancer from 1820, at which time no planned operation was performed, to 1920 when the stage was set for what might be termed the modern era.

In the pre-anæsthetic era Jacques Lisfranc (1790–1847) of Paris was the first to perform a planned operation for cancer of the rectum. Lisfranc's operation was a limited excision of the lower end of the rectum from a perineal approach and was first performed in 1826. A few years later in a paper read before the Académie Royale de Médicine, he reported the results in 9 patients, 6 of whom survived and were more or less continent. This type of operation was performed in England by Hubert Mayo (1796–1852) of the Middlesex Hospital in 1833, and James Wardrop (1782–1869) in 1834, but the reported cases are few compared with those on the Continent. In Berlin Johann Dieffenbach (1792–1847) performed a similar operation in some 30 cases and in his textbook of operative surgery states that all survived the operation and remained well for a year.

With the advent of anæsthesia the circumstances of the operation became easier, but the risk of complications remained, particularly hæmorrhage and sepsis. The écraseur was introduced by C. M. E. Chaissaignac (1805–1879) of Paris to reduce hæmorrhage, but sepsis was formidable until the teachings of Lister gained ground. In 1874 Theodore Kocher (1841–1917), of Berne, introduced excision of the coccyx to improve the exposure and promote freer drainage. (This modification had already been used by A. A. S. Verneuil (1823–1895) in France for operation for imperforate anus.) Richard Volkmann (1830–1889) of Halle described improved results using the antiseptic methods in 1878.

While these advances were occurring on the Continent the position at home seems to be best summed up in the words of Thomas Curling (1811–1888), surgeon to The London Hospital and sometime President of the Royal College of Surgeons. In 1876 Curling wrote: "Excision of the carcinomatous rectum was practised formerly by Lisfranc and Dieffenbach and is resorted to in the present day by several German surgeons. I am unwilling to discourage any attempt to relieve so dire a disease as cancer of the rectum, but knowing the danger that must be incurred from hæmorrhage in the operation, the misery likely to ensue from incontinence of fæces as well as the prospect of early return of the disease, I cannot think that a chance even of a prolongation of life is worth acceptance on the terms offered of such an operation." Henry Smith (1823–1894), assistant surgeon to University College Hospital, was more dogmatic. Writing a few years earlier in a popular textbook of the day he states: "Some surgeons were a few years since in the habit of performing excision of the lower end of the rectum for cancer, but this proceeding must be looked upon as barbarous and unscientific and is now happily exploded from the catalogue of surgical operations."

However, a change was imminent and in 1876 the Royal College of Surgeons set as the subject of the Jacksonian Prize Essay "Treatment of Cancer of the Rectum, particularly as regards curing or relieving the patient by excision of the affected part". The prize was awarded to Harrison Cripps (1850–1923) then aged 26 and Demonstrator of Anatomy at St. Bartholomew's Hospital Medical School. His essay was based on 53 collected cases between 1826 and 1875. The mortality was 20% and the survivors were shown to have their lives prolonged. There was not a high proportion of incontinence. Sepsis, particularly peritonitis, was the main cause of death. All but 3 of the cases were from the Continent. Cripps was subsequently appointed to the staff of St. Bartholomew's Hospital and became a leading exponent of excision of the rectum. His operation is described in his textbook published in 1884, when he had treated 42 cases.

Perhaps unknown to Cripps, William Allingham (1829–1908) had performed his first excision of the rectum in 1874, ten years after he joined the staff of St. Mark's Hospital. Allingham described his operation in his textbook published in 1888. The operations of Cripps and Allingham held the field in England for the next twenty years. Although the technique of the operation was different, the scope was similar, and only suitable for growths in which the upper limit could be reached with a finger.

To return to the Continent, where we left Kocher and Volkmann showing improved results, Paul Kraske (1851–1930) a former assistant of Volkmann and later Director of the Clinic at Freiburg, had used the Kocher operation, but wanted a better exposure to reach higher growths

and to control hæmorrhage more easily. To do this, he made a new posterior approach removing the coccyx and part of the sacrum. The results were read to the 14th Congress of the German Society of Surgeons in Berlin in 1885. The new factor in the Kraske operation, which was based on 2 cases, was the posterior approach, but the Kraske operation does not exist as a set technique, nor did Kraske always do it the same way. This new approach was rapidly taken up by various Continental surgeons who added their own modifications. Julius Hochenegg (1849–1940), later to become Professor in Vienna, brought out the upper cut end as a sacral anus for which he designed an ingenious colostomy belt. Later he modified the operation further; after mobilizing the upper cut end he brought it through the anus, from which the mucosa had been removed. This "pull-through" method now goes by his name.

In 1892 W. H. Maunsell (1847–1895), Senior Surgeon at Dunedin, introduced a new approach to excision of the rectum. In his operation, designed for growths of the upper rectum, the rectum was mobilized through an abdominal approach, and then invaginated through the anus. The growth was excised and the cut ends anastomosed. Robert Weir (1838–1927), Professor of Surgery in Columbia University and an Honorary F.R.C.S., described a modification of Maunsell's operation in 1901. Weir excised the growth through the abdominal incision and then drew the cut ends through the anus, where the anastomosis was done.

Progress at home remained slow. The Kraske operation was performed in 1888 by F. T. Paul (1851–1941) of Liverpool, but even in 1897 the largest series to be recorded consisted of only 14 cases. It was at this time that Ernest Miles (1869–1947) appeared on the scene. Miles had been house surgeon at St. Mark's in 1895, and later was appointed Assistant Surgeon at the Royal Cancer Hospital. After a few years' trial, he considered that the recurrence rate following the various operations then practised for cancer of the rectum was too high. He decided that removing the rectum "as a tube" was insufficient, and that attention should be paid to the field of lymphatic spread. Miles performed his first abdomino-perineal excision fifty years ago, and published the first results in 1908. Two years later he gave a further account of his new operation at the Annual Meeting of the British Medical Association.

Mr. J. P. Lockhart-Mummery, Senior Surgeon to St. Mark's Hospital, had introduced various modifications of the existing operations, and was one of the earliest to perform the abdomino-perineal excision. However he considered that the operative mortality of the Miles operation was too high, and introduced an extended perineal excision which he first performed in 1915. Details of this operation were published in 1920.

At the Section of Surgery of the 84th Annual Meeting of the British Medical Association, both Miles and Lockhart-Mummery read papers describing their particular operations. Another speaker was George Grey Turner (1877–1951), later Professor of Surgery at Newcastle, who described the sacro-abdominal operation, which he had then done seven times. This operation has since been perfected in the hands of Mr. W. B. Gabriel, and is now known as the perineo-abdominal excision.

The year 1920 is a suitable date to conclude this history of excision of the rectum. The abdomino-perineal, the extended perineal and the perineo-abdominal operations had all been evolved. Later years were to see improved results from these operations and the introduction of the synchronous combined excision, and various modifications of the conservative resection and abdomino-anal operations.

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Benign Strictures of the Colon

By Peter Boreham, M.Chir., F.R.C.S.

Introduction

In June 1956 an old lady was admitted as an emergency to the Whittington Hospital with large bowel obstruction of some days' duration. She was treated initially by blind transverse colostomy to relieve the obstruction and recovered. Subsequent investigation showed a benign stricture of the colon near the splenic flexure, and this was resected with end-to-end anastomosis and the colostomy closed later. She has done well since then (Case 1). The specimen showed a stricture at the left end of the transverse colon, the rest of the bowel being normal. There was no clue to the ætiology of the stricture either on gross appearance or on microscopy, and her previous history and subsequent course are featureless. After a search, 4 similar cases were found to have been admitted to the Whittington Hospital under Mr. Neville Stidolph in the past six years, and Mr. O. V. Lloyd-Davies has kindly given me the details of a case, making 6 in all. They have the same features, suggesting that they may have a common ætiology: All occurred in females, the youngest being 59, and the eldest 73. None of them had had any history of diarrhœa or other bowel symptoms until the onset of the illness, which had lasted only a few days or weeks before they came to hospital. Each presented as an acute illness, usually with colicky abdominal pain and collapse at the onset, and with diarrhœa and vomiting and, in the case of 3 of them, the passage of blood *per rectum*.

Four cases were treated by resection of the affected colon, one of them in two stages, owing to the presence of obstruction. Another case had a laparotomy, but no resection, and the sixth case was treated conservatively. In each there was a localized stricture of the colon, which appeared to be inflammatory in nature and the outside diameter of the colon was decreased, there being no hypertrophy or thickening of the walls.

The strictures were either in the left end of the transverse colon, in the lower descending colon, or at the recto-sigmoid junction, all places where the colon normally has a small lumen. 2 cases had two strictures each, but in the others there was a single stricture. The longest stricture was about 6 in. (15 cm.) in length but most of them were less than 3 in. (7·5 cm.) long.

There was no question of malignant disease causing the stricture in these cases, 4 of them being proved by resection and histology, 1 by laparotomy and inspection of the stricture and its subsequent resolution; in the last, the stricture disappeared on conservative treatment, as shown on subsequent barium enemata.

Inflammatory strictures of the colon are known to occur in certain granulomatous conditions, notably regional colitis resembling Crohn's disease of the ileum, tuberculosis of the bowel and in ulcerative colitis. In all these there is always a longer history than there was in the cases now presented, there is more general upset and the results of resection are poor.

Crohn's disease of the large bowel is notoriously liable to recur at the anastomosis or elsewhere, giving rise to early or late complications. Neuman, *et al.* (1954) in reviewing 201 cases of regional colitis give a figure of 42% recurrences after resection. Tuberculous strictures of the large bowel are usually associated with long-standing tuberculosis elsewhere, and respond poorly to local resection of the bowel, unless full supportive and chemotherapeutic treatment is given at the same time. Similarly, ulcerative colitis gives poor results when treated by local excision of a short affected segment, the disease usually recurring in the remaining bowel within a few months.

So that clinically, these non-malignant strictures of the large bowel differ from the known inflammatory conditions which give rise to such strictures, both in the absence of previous symptoms and in their smooth convalescence, and subsequent freedom from trouble.

One of the cases died from a carcinoma of the bronchus two and a half years after resection, but had had no bowel trouble in the meantime. The 3 cases that were resected are well and free of bowel symptoms five years, three and a half years, and six months after the resection. The fifth patient remains well, with no bowel symptoms two years after the onset of symptoms from the stricture, which was not resected. The sixth case is well, with no bowel symptoms six years after laparotomy when her two strictures were inspected but not resected.

Case 1.—Female, aged 77.

Admitted in June 1956 with large bowel obstruction. Previous laparotomy elsewhere in March 1956 for acute dyspepsia showed no abnormality. Emergency transverse colostomy performed. Subsequent barium enema showed an inflammatory stricture near the splenic flexure (Fig. 1). This was resected in July 1956 and the colostomy closed later. Uneventful recovery and now free of



FIG. 1.—Barium enema of Case I showing a stricture in the left end of the transverse colon.

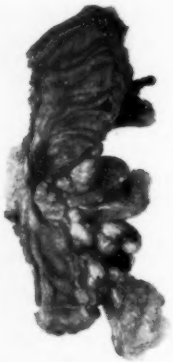


FIG. 2.—The specimen excised from Case I.

bowel symptoms. The excised specimen is shown in Fig. 2. Section showed ulceration of the mucosa with inflammation and fibrosis of all coats of the bowel.

Case II.—Female, aged 73.

Admitted in September 1953 complaining of abdominal pain and vomiting for five days, with diarrhœa for two days. No previous history of bowel trouble. Barium enema showed a stricture in the descending colon. Left hemi-colectomy in October 1953. Uneventful recovery. No further bowel symptoms until she died in January 1956 of carcinoma of the bronchus. Section of the colon showed ulceration of the mucosa with inflammatory changes in all coats of the bowel.

Case III.—Female, aged 73.

Admitted in January 1953 with seven weeks' diarrhœa and colicky pain of sudden onset. Barium enema showed long inflammatory stricture in the descending colon. Left hemi-colectomy in March 1953. Uneventful recovery with no bowel symptoms since. Section showed ulceration of the mucosa with plasma cell infiltration of all coats of the bowel.

Case IV.—Female, aged 62.

Admitted to Middlesex Hospital June 1948 with incomplete large bowel obstruction. Left inguinal colostomy performed for an inflammatory stricture in the sigmoid region. Barium enema confirmed the presence of a benign stricture. Refused operation until September 1953 when the stricture was still present and was resected by Mr. O. V. Lloyd-Davies. Section showed fibrosis only. Further laparotomy required 3 months later for small bowel obstruction due to adhesions, but thereafter uninterrupted recovery and no further bowel symptoms.

Case V.—Female, aged 64.

Admitted in September 1951 with forty-eight hours' colicky pain, vomiting and diarrhœa with melæna. Barium enema showed two strictures, one on either side of the splenic flexure, both appearing to be inflammatory in nature. Laparotomy showed two areas of narrowing and fibrosis of the colon with petechial hæmorrhages. Rest of bowel normal. No suggestion of malignancy. No resection. Recovered; no bowel symptoms since.

Case VI.—Female, aged 68.

Admitted in July 1954. Colicky pain, vomiting and diarrhœa with streaks of blood and mucus for three weeks. Barium enema showed two strictures, one in the lower sigmoid and one near the splenic flexure, each being 3–4 cm. long with tapering ends. Symptoms rapidly improved on conservative treatment, and she has had no bowel symptoms since. Two further barium enemas have been quite normal.

DISCUSSION

Clinical.—All these cases were comparatively fit for their age before the onset of the acute illness which brought them to hospital. There was no history of major tuberculosis in any of them, and none of them had had previous diarrhœa or intestinal upset. One of the cases was anæmic on admission and required transfusion, but although three of them had passed blood *per rectum* immediately before admission, there was no evidence of a long-standing blood loss.

Rectal examination was normal in all cases, but unfortunately not all of them were sigmoidoscoped. The rectal mucosa was normal, however, in the 2 that were, and in the other cases, the mucosa was seen to be normal in the colon either side of the stricture after resection.

X-rays.—The X-ray appearances of these strictures as shown on barium enema, have several features in common. The length of the strictures varies from a few centimetres to a few inches, and most of them would be considered rather longer than is usually seen with a carcinoma, and certainly longer than the short, narrow strictures usually seen in cases of healed tuberculous and ulcerative colitis.

The lumen of the colon at the stricture is, in most cases, between a half and one centimetre in diameter, and it is remarkable that in only one of these cases was an emergency operation required for complete obstruction. The ends of the strictures are, in most cases, clearly tapering and in none of them is there any well-marked shoulder deformity or filling defect, as usually seen with a malignant stricture. As noted above, they all occurred in portions of the colon which are normally narrow. In 2 of the cases small diverticula were present, but in neither case did they seem to bear any relation to the stricture. In all the cases, the colon away from the region of the stricture was normally haustrated and showed none of the "lead-pipe" appearance usually seen in ulcerative colitis.

Pathology.—In the 4 cases that were resected and also the stricture that was inspected at laparotomy, but not resected, the colon at the site of the stricture was reduced in its outside diameter and the wall of the colon was thinned and fibrous and showed no signs of thickening or hypertrophy. The serous coat was reddened and inflamed in each case, and the changes merged gradually into the normal colon on either side. In none of the cases was there much hypertrophy of the colon proximal to the stricture, suggesting that the stricture had not been present for any great length of time. None of the strictures was adherent to neighbouring peritoneal surfaces, and in no case were there more than a few small mesenteric glands.

On histology, the common features were ulceration of the mucosa, infiltration of the submucosa and muscle coats by polymorphs and small round cells, and a variable amount of fibrosis. The vessels were engorged but in all cases there was a striking absence of histological features which would give a clue to the ætiology. There were no giant cells to be seen or any giant cell systems with endothelial cells suggestive of either Crohn's disease or tuberculosis. There were no polypi or pseudo-polypi associated with the strictures in any of the cases, nor any diverticula in the neighbourhood of the stricture. In one case there was a considerable infiltration of all coats of the colon by plasma cells and in another case there is a complete disruption of the muscularis mucosa suggesting that the condition may be traumatic in origin.

On reflection, it seems possible that these cases may have a traumatic origin, certain other features, besides the histology, being in keeping with this. Chief among these is the sudden clinical onset, with colicky pain, vomiting and collapse, followed by diarrhœa and the passage of blood. I think the trauma could be caused by a scyballus passing through the narrower portions of the colon under a greater-than-usual stimulus, either from a purgative or an attack of gastro-enteritis.

Another possible form of trauma in one case was the passage of a gallstone through the narrowed colon, but there is no direct evidence obtainable to confirm this. The benign course of the disease, again, is suggestive of a traumatic stricture rather than a specific inflammatory disease, and so is the lack of surrounding adhesions or signs of associated localized peritonitis.

These arguments are not entirely convincing, however, but in the absence of other obvious ætiological factors, it seems conceivable that such a mechanism may account for these strictures.

Literature.—A search of the literature for reports of similar cases has not been very rewarding. Butler (1953) reported 3 cases similar to mine, which he called "Segmental colitis". 2 of these were treated by resection and 1 had a laparotomy only. All made a good recovery with no recurrence. Thompson (1950) reported one case, in which there was an inflammatory stricture in the proximal end of the transverse colon. The stricture was 5 in. (12·5 cm.) long and presented as an acute illness. Histologically he remarked on the absence of fibrosis in the wall of the bowel.

At the January 1957 meeting of this Section, Mr. Rupert Corbett (1957) reported the case of a labourer, aged 36, who developed a stricture of the colon looking very much like my cases on X-ray, but extending from the splenic flexure to the sigmoid. This portion of the colon was resected with an uneventful recovery and no further bowel trouble. It followed some weeks after a fall on to his left side from a height of 14 ft. There had been generalized collapse at the time, with bleeding from the rectum, and later, he complained of passing ribbon-like stools. It was suggested that this stricture followed either an indirect injury to the colon at the time, or possibly a traumatic thrombosis of the vessels in the mesocolon.

Mr. R. V. Cooke reported two similar strictures, one following six months after reduction

of a hernia, and another after reduction of an intussusception, and he suggested that they were due to venous thrombosis following the trauma.

There is a very large literature on the subject of "Segmental inflammatory disease of the large bowel", and this was well reviewed by Professor Charles Wells in 1952. He distinguishes three conditions, namely regional ileitis, ulcerative colitis and segmental colitis, and he compares the latter to Crohn's disease of the ileum, and remarks on the presence of a "cobblestone" appearance of the mucosa of the colon. He emphatically states that this is not a variant of ulcerative colitis.

Brooke (1954) in his book on "Ulcerative Colitis", and in his numerous other writings on the subject, refers to a right-sided disease, "ileo-colitis", which may occur segmentally; but he lays no great emphasis on segmental disease in the left side of the colon. He says that strictures following ulcerative colitis are most common in the rectosigmoid, and all his cases with strictures similar to those that I am presenting had long-standing diarrhœa, with loss of weight and other systemic upset, and, in fact, all the general symptoms associated with generalized ulcerative colitis.

Neuman and Dockerty (1954) reviewed the pathology of regional segmental colitis. They described it as "a non-specific granulomatous condition, with ulceration and thickening of the wall, occurring both in the colon and in the ileum, and characterized histologically by the presence of tubercles and giant cells".

Neuman *et al.* (1954) reviewed 201 cases of regional segmental colitis, and found that 14 of them had strictures; but each of these cases had signs of generalized disease, namely fever, diarrhœa and loss of weight.

There are numerous other papers reporting large numbers of cases and reviewing the subject of colitis, some of them presenting obvious features suggesting an ætiology similar to that of Crohn's disease and others resembling more closely the usual generalized type of ulcerative colitis. Many of them refer to the occasional occurrence of strictures of the colon, and I have made no attempt to review the whole of this literature. Of those referring to strictures or stenosis of the colon, however, only the 3 cases reported by Butler (1953) the 1 case reported by Thompson (1950) and those mentioned in our January 1957 meeting have, in common with my cases, the absence of any general upset, an acute onset of the disease, localization of the disease to a short segment of the colon, the rest of the colon being quite normal, and absence of complications after resection.

I wish to express my gratitude to Mr. Neville Stidolph for allowing me to operate on Case I and report his other cases, and to Mr. O. V. Lloyd Davies for giving me details of Case IV. Also to Dr. S. Robinson who reported on most of the specimens and Dr. Gordon Osborne who did the barium enemas. I am also very grateful to Dr. Basil Morson of St. Mark's Hospital for much helpful advice and criticism.

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Pelvic Abscesses: Diagnosis and Treatment

By HAROLD DODD, Ch.M., F.R.C.S.

SINCE the war, the paradoxical term, "a dying disease", has come into the medical vocabulary. It applies to tuberculosis, osteomyelitis, pneumonia and rickets. Impressions are often erroneous and I was tempted to regard pelvic abscess as a dying disease, until I looked up my records and found that whereas before the war (i.e. before antibiotics and sulphanilamides were available) I saw four a year; to my surprise, since the war I have treated three such abscesses a year. Thus, pelvic abscesses are still with us in general surgical practice. Further, they are missed often enough by registrars and residents for your Council to believe that they merit review in a short paper. There are few operations more satisfactory than that of draining a pelvic abscess through the rectum.

Collections of pus in the pouch of Douglas or in the rectovesical pouch occur after any abdominal condition, especially infected ones, with or without operation. They especially follow a ruptured appendix, less often a perforated peptic ulcer, partial gastrectomy for a penetrating ulcer, salpingitis, hysterectomy or suppurative diverticulitis, and very rarely after infective arthritis of the hip. Of every 4 cases, 3 are caused by suppurative appendicitis with peritonitis, while the fourth is due to one of the other causes, especially perforated or

penetrating peptic ulcer. Rarer cases are after anterior resection of the recto-sigmoid, and infection from Crohn's disease tracking down from the terminal ileal peritoneal fold.

A pelvic abscess may follow appendicitis, treated by operation or medically. One large abscess treated contained three pints of pus; it complicated appendicitis treated by aureomycin and terramycin. The temperature was swinging, the abdomen distended, and the patient had a moderate degree of diarrhœa which was thought to be due to the antibiotic. The period of three weeks and three days which passed without it rupturing is noteworthy; he had been ill four days before admission to hospital (Fig. 1).

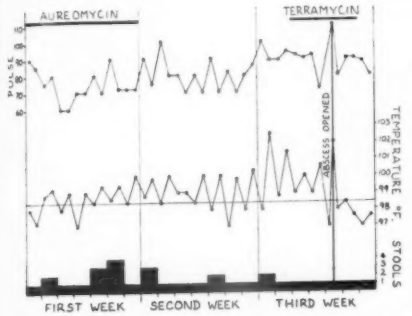


FIG. 1.—The chart of a man with appendicitis treated medically. The opening of the appendix abscess resolved his attack.

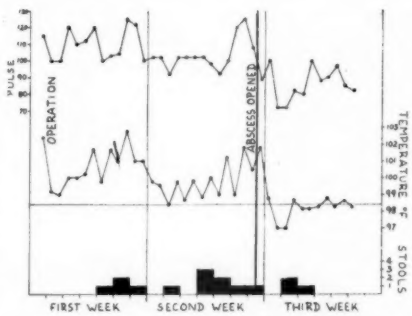


FIG. 2.—A pelvic abscess following appendicectomy. It ruptured spontaneously on contact with the examining finger.

Diagnosis.—The diagnosis of a pelvic abscess is based on the awareness of its possibility after any infected abdominal procedure, the temperature, diarrhœa and the rectal findings. The symptoms at first seldom direct attention to the rectum. The usual story is as follows:

After an infected abdominal operation, the chart shows a raised pulse and pyrexia for three to seven days. Then a normal temperature for one to three days, after which it starts to swing again. The pulse is in the 80 to 100 bracket and the respirations are unaffected, which tends to negative a subphrenic or respiratory infection, which are possible causes of pyrexia. The patient looks toxic. The tongue is moist, pointed and often shiny and bright red; a glossitis, which I have learned indicates undrained pus.

The bowel action.—After two to three days of further pyrexia, tenesmus and frequency and looseness of the bowels appear—perhaps two to four actions daily of fluid fæces, usually with an excess of mucus. This is regarded as satisfactory, as it follows the constipation usual after an abdominal operation. Occasionally the bowels continue inactive, or act once a day.

The abdomen is slightly distended in the lower half, and muscle tension is a little increased. The respiratory excursion below the umbilicus is absent, or even reversed. There is tenderness in the right iliac fossa, and the wound is often infected. As the pelvis fills, pus ascends on the left side, and tenderness appears here. In a thin patient, visible peristalsis is sometimes observed, which raises the possibility of post-operative subacute intestinal obstruction; this suspicion is strengthened when, as occasionally happens, the patient vomits. I think, however, that if there is the possibility of "pus somewhere", this should be sought before considering an organic intestinal obstruction.

Frequency and dysuria.—In the male it is readily understandable that with the bladder forming the boundary of an abscess, uneasiness, frequency, urgency and difficulty of urination will occur and may be the main complaint.

Rectal examination.—The diagnosis of a pelvic abscess is clinched by a rectal examination. The findings are according to the development of the abscess when the examination is made. Three stages may be found:

First stage: "The early and suspect phase." The rectum is empty, dilated, warm, and the mucous membrane is smoother than usual. At the tip of the finger, the rectal wall anteriorly and laterally is hard and indurated. There is no fluctuation, and the impression formed is that the dilated rectum is "set in felt".

Second stage: "The abscess is declared." A day or two later, a significant addition appears; it is the first sign of softening of the rectal wall, and the abscess will point through it. At the tip of the examining finger on the anterior wall, a dimpling or fluctuant spot is felt.

The sensation to the pulp of the finger is identical with that of palpating the tip of the nose, where there is a soft spot between the cartilages. The abscess is drained through this dimpling spot. The reflection of the peritoneum is a finger's length from the anus and it is necessary to press up firmly over the swollen valve of the rectum to reach the abscess.

Third stage: "The abscess is obvious." The fluctuating mucous membrane is bulging into the bowel lumen and there is an obvious abscess pointing into the bowel.

Fourth stage: The abscess may rupture. Spontaneous rupture of the abscess should rarely occur (it should be detected clinically before this). The pus bursts into the rectum, and is passed into the bed-pan after an urgent call to stool. Rupture, however, may not occur for two to three weeks.

Unusual presentations.—There are three unusual presentations of pelvic abscesses: First, a gluteal abscess: as the abscess points into the rectum it infects the pelvic cellular tissue. Ordinarily this is so indurated that spread is limited, but in a debilitated patient pus may track outwards and downwards through the sacro-sciatic foramen and point at the fold of either buttock. The process is a painless one, and in a patient who is not progressing and who obviously has "pus somewhere" vigilance is necessary to detect such a collection. I have seen this twice.

The second possibility is the abscess which tracks along the round ligament or the vas deferens and points in the groin at the pubic tubercle. I have had 3 patients with this presentation, and the abscess needed opening three times in one.

The third route is through the vaginal fornix. I have seen two in thirty years, and both followed a ruptured ectopic gestation.

Treatment: opening a pelvic abscess.—It is *in*advisable to open the abscess in bed, although occasionally one's finger penetrates the bowel wall effortlessly (Fig. 2). The patient is anæsthetized, placed in the lithotomy position and catheterized. I once mistook a full bladder for a pelvic abscess and withdrew urine with the aspirating needle.

The operation.—A duckbill speculum is inserted into the anus taking care not to tear the anal mucosa. The rectum is usually empty, but if not, it is cleansed of fæces. The dimpling or fluctuating spot on the anterior wall is located with the tip of the left index finger, and a long wide-bore needle attached to a 20 c.c. syringe is thrust resolutely through this softened area in the rectal wall; pus appears on aspiration. A hesitant approach may impale the mucosa on the needle point and fail to enter the abscess. If no pus is found, the point of insertion of the needle is checked to see that it really has penetrated the rectal wall at the fluctuating area. If no pus is withdrawn, the operation is stopped. When pus is located, the syringe and needle are kept in position. A pair of uterine dressing forceps, whose points are grooved on the inside, are slid along the needle through the rectal wall and into the abscess cavity. Pus emerges, often considerable in volume and smell. As the flow slows, the forceps are opened in a north-and-south and east-and-west direction, making a generous hole in the rectal wall. I no longer insert a drain, and patients have done well. I once used a pair of Mayo scissors to open an abscess, and a gross hæmorrhage followed which exsanguinated the patient, and required a second operation and a transfusion two hours later. I think I cut a vessel in the rectal wall while opening and closing the scissors. No incidents have occurred since using the uterine dressing forceps.

After-care.—A glycerin suppository is inserted into the rectum daily for four days. The pus is cultured for its sensitivity and if necessary the appropriate remedy is given; very rarely actinomycosis will be found, but as a rule, the temperature falls immediately the abscess is drained. Hæmoglobin estimation often reveals a surprising degree of anæmia and this is corrected. No patients have died.

DISCUSSION

In the ensuing discussion instances were given of pelvic abscesses rupturing into the bladder, following the psoas sheath in the thigh, and penetrating levatores ani and pointing in the ischio-rectal fossa.

The President recounted 2 patients with undetected pelvic abscesses complicating carcinoma of the ovary and uterus. Examination under an anæsthetic is valuable.

The development of acute intestinal obstruction with pus in the pelvis was cited.

The use of antibiotics in preventing and treating residual abscesses was discussed but opinion favoured drainage whenever pus was detected.

MR. A. LAWRENCE ABEL and Mr. H. GORDON UNGLEY
showed a coloured talking film entitled:
Hæmorrhoids or Piles and the Early Detection of Rectal Cancer.

Section of Dermatology

President—LOUIS FORMAN, M.D., F.R.C.P.

[*March* 21, 1957]

Dermabrasion

By J. S. PEGUM, M.D., M.R.C.P.

DERMABRASION is a technique of considerable if not of respectable antiquity. As Burks (1956) points out the Ancient Egyptians probably used pumice and alabaster for this purpose. The modern form of dermabrasion was introduced and developed by Kromayer (1905) in Germany. In the United States abrasion became popular after Iverson (1947) had introduced the sandpaper technique; later Kurtin (1953) revived and popularized the Kromayer technique of using rotating machinery to produce what Kurtin described as "Corrective Surgical Planing of the Skin". In England, on the other hand, dermabrasion has lagged behind and tends to be treated with suspicion.

I started planing in 1954 after the technique had been introduced at the London Hospital by my senior colleague Dr. Brian Russell. In all I have done 41 planings on 24 patients. These are small numbers compared with those of Kurtin and of Burks in America, both of whom have reported series of 1,000 planings. The apparatus which we use consists of an electric motor capable of 18,000 r.p.m., the speed of which can be varied by a foot-operated rheostat. The drive is through a flexible cord and a ball-bearing mounted handpiece, which carries the abrading instrument, a toothed wheel made of steel (Eller and Eller, 1956). The skin is frozen with a spray of Arcton (or Freon) to produce local anæsthesia and a firm surface for abrasion. Arcton (or Freon) is a mixture of fluorinated hydro-carbons; its local effects are similar to those of ethyl chloride but it has the advantage of being non-inflammable and non-toxic.

Conditions for which I have used this technique are as follows:

Artistic tattoos (3 *cases*).—Two were on the forearms and were removed satisfactorily. The cosmetic results although acceptable to the patients were far from perfect because the flexor aspect of the forearms does not re-epithelialize nearly so elegantly as the face and also because the tattoo material was deeply ingrained. The third case was a dark-skinned West African with a tattoo-mark on the forehead. After planing the skin re-grew quite white; later the pigmentation appeared to be spreading out from the mouths of the hair follicles at which stage unfortunately the patient defaulted. This case, although incompletely reported, illustrates the dangers already well recognized of producing dyschromias in dark-skinned persons.

Accidental tattoos (4 *cases*), produced by the entry of road or coal dirt into breaches of the skin. The tattoos were removed adequately but two cases developed keloids which required further treatment.

Post-acne scarring (6 *cases*).—This is one of the principal indications for dermabrasion. The results show improvement rather than cure. The improvement is gratefully accepted by the patient.

Other scars (1 *case*).—A woman of 50, who had a scar with bridgework on the neck at the site of previous lymph-gland suppuration. The treatment produced improvement.

Nævus flammeus (3 *cases*).—The results are promising but vary from patient to patient and from area to area in the same individual.

Adenoma sebaceum (2 *cases*).—The lesions treated were flattened by dermabrasion.

Lichen sclerosus et atrophicus (1 *case*).—The early result here is distinctly promising. If local cure can be effected by abrasion, it may be a useful treatment in sites where leukoplakia is likely to follow.

Infected sebaceous cyst (1 *case*).—The cyst was unroofed or "marsupialized", the floor becoming part of the external skin. This appears to be a useful treatment. It is similar in principle to using dermabrasion in the active phase of cystic acne.

Chronic discoid lupus erythematosus (1 *case*).—A lesion was planed twice and on each occasion healed well and became covered with normal skin. Unfortunately relapse occurred promptly after each treatment.

Linear nævus (1 *case*).—A lesion was planed twice and on each occasion recurred.

Alopecia areata (1 *case*).—Planing produced no improvement.

Other conditions in which dermabrasion is reported to be of value include rhinophyma, rosacea, freckles, vitiligo and shagreen skin.

I have encountered the following complications: milia, keloids, dyschromia, atrophy of the skin, and (in 1 case) hæmorrhage (fortunately not severe in degree).

On the basis of a limited experience it is not possible to assess accurately the value of the procedure. Probably, however, dermabrasion will remain as a useful treatment for a limited number of conditions and will take its place beside the other physical methods now used by the dermatologist.

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Dermabrasion

By PATRICK CLARKSON, M.B.E., F.R.C.S.

THE value of dermabrasion, by wire brushes or by other methods, is disputed. Thus Dr. George V. Webster (1956) of California, in a lecture at Guy's Hospital, stated that the effect of dermabrasion depended on the length of the time of the follow-up; the longer the interval after operation, the worse the result. My own view, based on over three years' use of Kurtin's wire brushes and Eller's abrasive wheels and a longer experience of abrasion by the cruder, now generally abandoned, method of sandpaper is more optimistic (Clarkson, 1949). I believe the failures and adverse results which have been widely seen in the States and elsewhere have been largely due to indiscriminate use of the method under inadequate surgical conditions.

In particular it should be remembered that this technique for the improvement of appearance is only one of a number of techniques which can be used for the same end. The best result can often only be obtained by a combination of abrasion with excision of some lesions, or more often by a general tension of the cheek (as is provided by the standard ridectomy techniques). The question of diagnosis of depth of ingrained dirt, or tattoo pigment, also affects the proper choice of technique. Depth can sometimes only be assessed accurately during the course of planing through the affected area of skin. It not infrequently happens that the whole depth of skin has to be removed. The operator then has to make a decision whether to use a surgical method of closure or to allow healing by marginal ingrowth with a risk of keloid or other formation of gross unsightly scarring. What I would like to plead is that for the great majority of lesions where wire brush abrasion can be of value the operator must be technically capable of supplementing the method by such additional plastic methods as may be necessary for the best results. It is for these reasons that I plead that the method be used only under full operating theatre conditions, not in the inadequate arrangements of consulting rooms.

The use of Freon (Eller and Eller, 1956) and other freezing agents as the anæsthetic also raises important points for debate. Freezing (Smith, 1954) causes intracellular dermal rupture, and Pomerat and Lewis (1953) have shown by tissue culture methods the added burden that this causes to normal healing. Nor do English patients take well to the freezing of large areas of the face; nor can freezing be considered really safe for use near the eyes. For these and other reasons I prefer local analgesia for small areas; a general anæsthetic is preferable for the most extensive cases. I would especially stress the need for repeated abrasion for many of the acne cases. Nor is it necessary to await the disappearance of acute lesions before proceeding to abrasion in acne scars. Indeed the abrasion appears to accelerate the resolution and disappearance of the active lesions. But I must stress that my experience is limited to abrasion of acne scars in the presence of only a few active lesions, not when any diffuse severe reaction is present.

There are also reasonable matters for debate about almost every aspect of the abrasive techniques at present used, about the type of abrasive wheel, the rate of revolutions per minute of the wheel, the type of post-operative dressing, as well as about the range and scope of method. My own view is that dermabrasion is capable of dramatically successful results in a minority of patients (such as small superficial angiomata), and can give a very reasonable margin of improvement to many other patients (such as girls with acne scars, provided it is repeated two or three times); but it can be harmful and has some special complications of its own. This especially holds if it is not used with technical skill.

While minor areas can be successfully abraded under local anæsthesia on an out-patient basis, extensive facial operations can I believe only be safely done under general anæsthesia in an operating theatre with adequate post-operative nursing as an in-patient for two or three days. If these precautions are not observed, the method is likely to fall into the disrepute in England that prevails for it in many parts of America.

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Tuberculides.—O. L. S. SCOTT, M.R.C.P.

This is an otherwise healthy young woman aged 26 with a papular, erythematous rash on her face and forearms. The rash has been present on the face for more than six years, and is getting worse. Biopsy taken when she was first seen two years ago showed (Dr. Ian Whimster) "tuberculosis, with the lesions apparently arranged about the hair follicles".

The Mantoux test was positive at a dilution of 1 : 1,000 Old Tuberculin. X-ray of chest showed multiple, small, well-defined opacities in both middle and lower lobes, consistent with a diagnosis of sarcoidosis.

A diagnosis of miliary sarcoidosis was considered, and she was given intensive treatment with streptomycin, isoniazid, calciferol, prednisone and chloroquine. (The last was given since she is extremely sensitive to actinic light.) All these drugs failed to help, and some of them made her feel ill. No improvement in skin or lung has been noted.

In view of the increasing erythematous background to the eruption, a diagnosis of micropapular tuberculide (rosaceous tuberculide of Lewandowsky) was made and approved at another dermatological clinical meeting. Her condition remained unchanged until six weeks ago when she developed a crop of papules on the forearms which resemble papulonecrotic tuberculides. Histology of one of these papules is consistent with this diagnosis (Dr. Henry Haber).

The sudden appearance of these lesions at least five years after her original facial eruption is unusual. I have been unable to find any evidence in the literature of micropapular tuberculides associated with subsequent papular necrotic lesions elsewhere.

Dermal Leishmaniasis.—R. G. HOWELL, M.R.C.P.

Mr. S. T., aged 23, an Indian national from N.W. India, resident in England twelve months. Eight months ago he developed a papule on the dorsum of the left wrist which has increased in size. Five weeks ago a similar lesion began on the left internal malleolus.

On examination.—General health good. On the dorsum of left wrist a raised red-brown granulomatous lesion 3 cm. × 5 cm. On the left internal malleolus a similar papular lesion 1 cm. in diameter.

Investigations.—Hb 106% (16·2 grams/100 ml.). W.B.C. 15,000 (polys. 74%, eosinos. 0%, lymphos. 23%, monos. 3%). Blood W.R. and Kahn negative. Chest X-ray: No abnormality. Scraping: No Leishman-Donovan bodies seen. Leishmanin intradermal test: At 48 hours: papules 3 mm. in diameter; surrounding erythema 10 mm. in diameter.

Biopsy (Dr. H. Haber).—Chronic granulation tissue consisting of tuberculoid structures and diffuse round cell and endothelial infiltration. No organisms or L-D bodies seen.

Comment.—This patient has been resident in an endemic area and the Leishmanin test is positive. No *Leishmania tropica* have been found in scrapings or sections from the wrist lesion. It appears that in older lesions where tuberculoid granulation tissue has replaced the initial reticulo-endothelial cell response to the parasite, *Leishmania tropica* may be difficult to find.

He is being treated by mepacrine injections (0·1 gram mepacrine in 1 c.c. distilled water) into the lesions, which are beginning to resolve.

The **President:** The organism should be demonstrated in section from the soft granulomatous type of dermal leishmaniasis.

Dr. **H. Haber:** I think another biopsy will reveal it from a non-ulcerated area.

Dr. **C. D. Calnan:** I saw quite a large number of these cases in Northern India during the war. I accept the fact that in some cases it is difficult if not impossible to find the organism. The leishmaniasis lesions are sometimes divided into the ulcerative variety, in which organisms are found easily, and this small granulomatous form in which they may be absent.

Sarcoidosis with an Unusual Arthritis.—C. M. RIDLEY, B.M., M.R.C.P. (for J. S. PEGUM, M.D., M.R.C.P.).

H. L., female, aged 26.

This patient was well until 1951. At that time and again in 1952 and 1954 she had febrile illnesses with pain and swelling of the joints and glandular enlargement. Between the attacks she felt well and the glands became smaller; there was residual stiffness in some joints. During the first illness the spleen was felt once. That in 1954 was associated with a dental abscess. Each attack settled within a few weeks without treatment. In 1953 she had a normal pregnancy. Since 1951 she has also had occasional urticaria.

Investigations (1951).—Chest X-ray normal. Hb 67%. W.B.C. 12,200 (polys. 84%, lymphos. 13%, monos. 3%). E.S.R. 64 mm. in the first hour (Westergren). Sternal marrow normal. Paul Bunnell test negative. Wassermann reaction and gonococcal fixation test negative. Agglutination tests for *B. typhosus* and *paratyphosus*, salmonella and brucella negative. Blood culture negative. Plasma proteins: Total 6·9, albumin 4·5, globulin 2·4 grams%.

Biopsy of cervical gland. Marked hyperplasia of lymph node with development of active germinal centres. An intense proliferation of reticulum cells and immature lymphoid cells is present in the pulp of the node. This proliferation is of uncertain nature and might represent either the start of a neoplastic lymphadenopathy or the early proliferative response of normal immunity.

Investigations (1952).—X-ray of feet normal. Hb 80%. W.B.C. 19,400 (polys. 81%, lymphos. 15%, monos. 3%, metamyelocytes 1%). Gonococcal fixation test and meningococcal fixation test negative. Blood culture (4 times) negative. Culture of axillary lymph gland for acid-fast bacilli negative.

Biopsy of axillary lymph gland. Lymph node showing hyperplasia of germinal centres, proliferation of sinus endothelium and of reticulum cells and histiocytes of pulp. Scanty infiltration with eosinophils. This suggests a non-specific chronic inflammatory reaction.

Investigations (1954).—X-ray of hands: Early erosion and sclerosis of articular surfaces. Hb 76%. W.B.C. 11,200 (polys. 82%, eosinos. 2%, lymphos. 10%, monos. 6%). E.S.R. 74 mm. in the first hour (Westergren). Rose's test negative. Agglutination test for brucella negative. Plasma proteins: Total 7·1, albumin 4·2, globulin 2·9 grams%. No L.E. cells found in the blood.

At the end of 1956 a rash appeared on the trunk. The last menstrual period was in January and she is probably pregnant.

On examination.—Looks well. C.V.S., R.S., A.S.—n.a.d. Eyes—n.a.d. L.S.—no glands felt. Joints—limited dorsiflexion of the wrists.

Skin: Keloidal scar at the site of sternal puncture; biopsy scars not keloidal. Back, and to a lesser extent on the abdomen, buttocks, arms and thighs: densely scattered red papules, smooth surfaced, showing a faint brownish discoloration on diascopy and some surrounding diffuse erythema. No dermographism.

Investigations (1957).—Chest X-ray normal. X-ray of hands: Loss of cartilage in the wrist-joints. X-ray of feet normal. Hb 86%. W.B.C. 8,800 (polys. 68%, eosinos. 1%, lymphos. 28%, monos. 3%). E.S.R. 22 mm. in the first hour (Westergren). Plasma proteins: Total 7·6, albumin 5·0, globulin 2·6 grams%. Mantoux test negative. Beryllium patch test negative.

Skin biopsy.—Dermal granuloma consistent with sarcoid. Compact aggregates of large epithelioid cells. No necrosis. Occasional lymphocytes. No doubly refractile material. No acid-fast bacilli seen.

Comment.—At the time of her first two admissions the diagnosis of a reticulosis was made; since the admission in 1954, however, it has been considered more likely that she has either rheumatoid arthritis or systemic lupus erythematosus. She now has sarcoidosis which seems to be limited to the skin.

It may be that the conditions are unrelated, but a connexion between them is possible.

It seems agreed by writers on the subject—for instance Longcope and Freiman (1952) and Cowdell (1954)—that the joints are rarely affected in sarcoidosis apart from the joint pains accompanying associated erythema nodosum. Cases of sarcoidosis and arthritis have, however, been reported. Burman and Mayer (1936) described a case with a synovial biopsy; Castellanos and Galan (1946), Myers *et al.* (1952), Gendel *et al.* (1952) and Laroche *et al.* (1955) described others. All these cases have, however, had evidence of concurrent sarcoidosis elsewhere, whereas in this patient sarcoidosis has appeared in the skin six years after the onset of the illness involving her joints.

It is likely therefore that she shows only an interesting chance association of sarcoidosis and an unusual arthritis.

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JOINT MEETING No. 4

Section of Neurology with Section of Psychiatry

Chairman—D. W. C. NORTHFIELD, M.S., F.R.C.S.
(President of the Section of Neurology)

[*May* 2, 1957]

DISCUSSION ON THE TOXIC EFFECTS OF DRUGS USED IN NEUROLOGICAL AND PSYCHIATRIC PRACTICE

Dr. Hugh Garland (Leeds):

Drugs Used in the Management of Epilepsy

It would be of some interest to know how many patients are being treated for epilepsy at any one moment, the incidence of epilepsy, very broadly defined, in Great Britain usually being considered to be about 250,000 persons. Through the kind co-operation of the Leeds Executive Council a group of general practitioners was circularized and information obtained relating to a population of about 300,000. 800 epileptic patients were reported to be under treatment, an incidence of 2·5 patients per 1,000 population. This suggests that the number of epileptics under treatment in Great Britian (population approx. 50,000,000) is about 125,000, which is perhaps only half of all epileptics.

My personal figures relate to a survey of over 2,000 epileptic patients seen in the Neurological Department of the General Infirmary at Leeds, and in private practice, between the years 1948 and 1956. The dominant problems arose in connexion with the hydantoins, the bromides, primidone and the diones. In this group only two examples of barbiturate intoxication were seen, which illustrates the wide margin of safety between the therapeutic and toxic doses of the barbiturates.

The hydantoins.—During the initial stages of treatment the signs and symptoms of intoxication with sodium phenytoin are the result of gastric irritation, giving rise to anorexia, nausea and vomiting, or to individual idiosyncrasy reflected in the skin by rashes which may resemble those of measles or scarlet fever. The former may be avoided by giving the drug after meals, whilst, if small doses are given initially and later increased, the incidence of dermatological complications is said not to exceed 5% (Tullidge and Fox, 1942; Symonds, 1950) and in my experience the incidence has been even less.

The most important toxic phenomena are referable to dysfunction of the cerebellum with resulting dysarthria, nystagmus and ataxia, with or without disturbance of mentation and behaviour. In 31 patients symptoms and signs of this nature occurred and were of sufficient severity to warrant admission to hospital. It was possible in only 4 to incriminate overdosage and in another 3, who developed their disability within the first few days of treatment, individual hypersensitivity seemed to be the predominant factor. The greater proportion, however, had received sodium phenytoin and phenobarbitone or phemitone (Prominal) for many years in unvarying quantities and had developed evidence of toxicity for no apparent reason. This would seem to indicate that either detoxication or excretion varies from time to time in any one individual and may occasionally lead to the accumulation of an excessive quantity of phenytoin. In others it is clear that there is a very narrow margin between the therapeutic and the toxic doses, and 6 patients developed toxic symptoms after their daily intake was increased from 3 to 4½ grains. More rarely the addition of primidone may provoke phenytoin toxicity although the dose of the latter drug is not altered.

Mental disturbances may accompany the cerebellar dysfunction or may occur independently. These vary from drowsiness which is rapidly controlled by amphetamine sulphate, to a confusional psychosis necessitating withdrawal of the drug. One of my patients developed an acute mania and had to be forcibly restrained; this was later followed by prolonged and severe depression, but fortunately such examples must be exceptional.

Spongy hypertrophy of the gums is usually a late complication and though superficially this may resemble scurvy it is probably unrelated to deficiency of ascorbic acid (Hawkins and Meynell, 1956). Symonds (1950) estimated the frequency of this toxic manifestation to be in the region of 15% but my impression is that the incidence is less than that. It may be that a lower figure has resulted from improvement in dental hygiene in recent years, since it has been claimed by Nattrass (1949) that hypertrophy may be associated with dental sepsis; in my experience, however, this is certainly not always true. Gum hypertrophy is reversible and may largely result from œdema; it rarely if ever occurs after the administration of other hydantoins and for this reason Mesontoin may be substituted for sodium phenytoin when gum hypertrophy proves troublesome.

Perhaps the most interesting late toxic effect, and the last to be recognized, is a megaloblastic anæmia. The first example of this was described by Badenoch in 1954. In a recent survey of the subject Gydell (1957) reviewed the problem of megaloblastic anæmia in patients being treated with diphenylhydantoin and primidone; 3 personal cases are described and 14 others mentioned from the literature between 1954 and 1957. All 17 were taking one of the hydantoins with the exception of 3 who were taking primidone alone. The duration of treatment had varied from thirteen years to nine months and the ages of the patients from 17 to 52, 12 being females. It was striking that the 14 quoted from the literature all came from England. What interests me still more is that I find that I first recognized this condition, without appreciating its importance, in 1948.

A woman of 28 had suffered from major epilepsy since the age of 3. For eleven years she had been taking sodium phenytoin grains 4½ and phenobarbitone grains 1½ daily; at one point Mesontoin was substituted for phenytoin because of gum hypertrophy but because of drowsiness the former treatment was resumed. One month before admission to hospital in 1948 she had complained of increasing lassitude. She was found to be anæmic, with Hb 58%, R.B.C. 2,900,000 and C.I. 1·0; a blood film showed macrocytosis, anisocytosis and poikilocytosis, the reticulocytes being less than 1%; the sternal marrow was actively megaloblastic. The gastric juice contained free hydrochloric acid and the split and unsplit fæcal fats were normal. Treatment with Anahæmin 4 ml. intramuscularly every day was without effect. Folic acid 30 mg. by mouth daily was followed by a reticulocyte response and both the peripheral blood and sternal marrow were rapidly restored to normal. Phenytoin had been withdrawn when the results of gastric analysis indicated that we were not looking at pernicious anæmia but six months after leaving hospital phenytoin treatment was resumed and has been maintained, without folic acid, up to the present time without any hæmatological relapse.

Since that time I have had three other examples of anæmia of a similar character resulting from phenytoin, though one of these has also received primidone, and my experience adds nothing, except numbers, to that of Gydell and others (Hawkins and Meynell, 1954, 1956; Chalmers and Boheimer, 1954; Rhind and Varadi, 1954; Webster, 1954; Berlyne *et al.*, 1955; Ryan and Forshaw, 1955). In a few of these recorded examples extensive investigation has shown that the serum B_{12} level and the absorption of folic acid were normal; all have responded to folic acid by mouth and only four to vitamin B_{12} by injection, though in the case of two of the latter the withdrawal of phenytoin may have been responsible for the improvement (Webster, 1954; Ryan and Forshaw, 1955) whilst one other (Chalmers and Boheimer, 1954) may have had coincidental pernicious anæmia.

Girdwood and Lenman (1956) and Girdwood (1956) described a similar anæmia attributable to primidone. They pointed out that phenytoin, primidone and phenobarbitone all have in common with folic acid a pyrimidine ring and they suggested that drugs with this structure might act as competitive inhibitors for some enzyme system involving folic acid as a co-factor. It is therefore important that Hobson *et al.* (1956) have described a patient who developed a megaloblastic anæmia attributable to large quantities of the two barbiturates Amytal (amylobarbitone) and Seconal (quinalbarbitone). In addition, Hawkins and Meynell in 1956 surveyed 159 epileptic patients from a colony and found that only one had a frank megaloblastic anæmia but 36% showed the mean corpuscular volume increased to between 94 and 114 cu.μ; the sternal marrow was megaloblastic in 5 and probably so in 1 other. The highest incidence of macrocytosis occurred in those taking phenytoin and phenobarbitone (45%) but when either phenobarbitone or phenytoin alone had been taken the figure was still in the region of 30%. Since reading their paper I have been carrying out routine blood counts on all patients taking these drugs but my figures at the moment are not significant.

The bromides.—It may cause some astonishment that the bromides should be invoked as a major cause of intoxication in the year 1957 but there is little doubt that many examples of bromism are overlooked as was emphasized by Spence (1957). This condition has been proved in 2% of epileptics seen in private practice though it amounted to less than 0·1% of hospital patients, many of whom were seen by doctors who did not entertain the likelihood of bromism and had in all probability never recognized an example. I have shown elsewhere

(Garland and Parsonage, 1951) how the consumption of bromide in the General Infirmary at Leeds fell from 2,297 lb. in the triennium 1939 to 1941 to only 10% of that level in 1948 to 1950, a trend which was accompanied by a proportionate increase in the use of barbiturates.

Although the bromides have rightly fallen into disrepute in the treatment of epilepsy they are still widely employed in combination with other drugs such as chloral hydrate and gelsemium for a supposed sedative or analgesic effect, which is a fallacy. It is interesting that in the General Infirmary at Leeds the consumption of bromide has remained stationary for the past seven years (100 lb. per annum) but I find that its use is strictly limited to the Department of Dermatology.

It is generally accepted that blood levels of 50–100 mg.% are necessary to produce a therapeutic action and since a dose of more than 50 grains provokes vomiting this level cannot be achieved by a single dose. It has been known for twenty years that repeated small doses of bromide are dangerous. The kidney excretes halogens without discrimination and retention of bromide at the expense of chloride steadily develops. Mental symptoms may appear with blood levels of 160–200 mg.% so that the margin of safety is too small for there to be any therapeutic value in prescribing the drug. Symptoms of intoxication are predominantly mental and consist of a dull headache with depression and slowing up of intellectual processes which may be erroneously attributed to psychoneurosis, and indeed it has been estimated that up to 10% of the inmates of certain American mental hospitals were suffering from no other illness than bromism. It is important to remember that the characteristic bromide rash is found in less than 25% of those suffering from intoxication. Less commonly with more profound bromide poisoning there may be manic psychosis, hallucinosis, dysarthria and ataxia. I have seen 29 examples of bromide intoxication between 1949 and 1957 and only 5 of these were epileptics, suggesting that the uselessness of bromides in the treatment of epilepsy is now fairly widely recognized, though their bogus position in other realms is still unknown or ignored.

There is a lessening of tolerance to bromide with increasing age. One of my patients, a woman of 60, had complained of headache and loss of weight for a month, and had become tearful, abusive and later deluded. The highest level of serum bromide recorded was only 160 mg.% yet when she was given a high salt intake and ceased taking her "medicine" her mental state rapidly returned to normal. This may be compared with a boy of 16 who had taken 15 grains of potassium bromide for several months on account of epilepsy; his mother complained that he was rather "dopey" though otherwise well. His serum bromide level was 225 mg.%, a much higher level than in the first patient but associated with only mild symptoms, as usually obtains in the young. It has generally been considered that levels of much over 400 mg.% are incompatible with life, but I saw one elderly woman who had taken a "nerve" medicine containing 10 grains of bromide for over twenty years and her blood level, at a time when she seemed to be dementing, was 505 mg.%; she made a rapid and complete recovery. It would seem that in the treatment of epilepsy, insomnia or tension states bromides share an equal status with their old contemporaries the leech and the seton.

Primidone (*Mysoline*).—The majority of the toxic effects of primidone, unlike those of the other anti-convulsants, occur during the first few days of treatment and indeed often after the first dose. Anorexia, nausea and vomiting are fairly common, especially if the drug is taken while fasting. Drowsiness is also complained of in about one-fifth of the patients and for this reason it is best to give the first dose in the late evening. Whitty (1953) reported drowsiness in 48 of 70 epileptics treated with primidone, but in only 12 was this sufficiently severe or lasting to necessitate withdrawal of the drug. Fortunately, both the gastro-intestinal symptoms and the drowsiness usually subside within a few days when therapy is maintained and the main problem is to convince patients of this, since many refuse to accept such a prognosis.

Whitty (1953) and Sharpe (1954) have reported acute confusional psychosis, with paranoid features, as a complication of primidone therapy. This is undoubtedly a valid observation but the advent of a psychopathy may not always be attributable to primidone alone. There is a high incidence of psychiatric deviation in patients with lesions of the temporal lobe, with or without epilepsy, and a fortuitous association in such patients treated with primidone must be expected. Hill and Falconer (1953) described 13 patients with epilepsy and psychopathy and in 11 of these there was EEG evidence of a focus in one temporal lobe. A second factor to consider is the phenomenon of convulsion dependence. It has been recognized for some time that psychotics who have occasional fits may obtain benefit from electric convulsant therapy and it is not uncommon to see pre-ictal irritability and tension relieved by the advent of a fit. Under these circumstances the suppression of fits may lead to a worsening of the mental state irrespective of the nature of the drug employed. However, bearing these considerations in mind, a few patients are totally unable to take primidone even in homœopathic doses. One patient, a woman of 22, had suffered from major convulsions, often with rotation of the head and eyes to the right, since the age of 3. She had been

treated with a number of drugs including Mesontoin, phenytoin, phenobarbitone and phemitone, with a very inadequate control of her fits. EEG showed a widespread abnormality without focal features and all other investigations, including air encephalography, were normal. She was given a single dose of primidone 0·25 gram and within a matter of hours developed a confusional psychosis with paranoid delusions; this resolved in thirty-six hours and she remained mentally normal until a second dose of 0·125 gram of primidone was administered, when the previous experience was repeated. In this case the time relationship made it clear that the psychopathy had been provoked directly by the drug. However, after a year in which she had no primidone she became permanently deluded and is now a certified psychotic. One other patient, also a young woman, developed a similar psychopathy with primidone which was not related to fit-suppression.

Many patients become very drowsy when a barbiturate is given with primidone and there seems to be a synergistic effect between these drugs in this respect. Skin rashes of morbilliform type have been reported by Whitty (1953) and Briggs and Tucker (1954) but they are uncommon. Acute primidone poisoning in a child has been reported by Morley and Wynne (1957), the child having swallowed at least fifty tablets. An interesting feature of this case was the appearance of crystalluria and recovery of consciousness was accompanied by temporary ataxia.

The diones.—The strange symptom of visual "glistering", was first described by Lennox in 1947, affecting about 2% of epileptics treated with troxidone (Tridione). This seems to be peculiar to troxidone and when troublesome may be relieved immediately by changing to another dione. It is exceptionally rare in children under the age of 6, perhaps because of their inability to describe the symptom. Another occasional complication is the appearance of acneiform papules over the forehead and face, and more rarely a generalized morbilliform eruption (Lennox, 1947).

By far the most important drawback to the use of the diones is their effect on the bone-marrow. Two distinct forms of blood dyscrasia occur. The first, which is not uncommon, consists of a slow downward drift of the neutrophil count, sometimes associated with a mild increase in the total eosinophils and lymphocytes (Davis and Lennox, 1947; Greaves, 1946; Briggs and Emery, 1949). This, provided it is detected in time by serial blood counts, is not dangerous and the normal white cell count is restored when diones are withdrawn. The second, which fortunately is rare and which I have not yet seen, is the sudden development of an aplastic anæmia with a rapid diminution of the circulating red cells, polymorphonuclear white cells and platelets (Harrison *et al.*, 1946; Mackay and Gottstein, 1946; Braithwaite, 1948; Forster *et al.*, 1949). I believe that all the recorded cases of aplastic anæmia have died of secondary infection and multiple hæmorrhages, together with one example of exfoliative dermatitis, and energetic therapy with hæmatinics, transfusion, antibiotics and the withdrawal of diones seems to be of no avail. Moreover, the condition develops too rapidly for serial blood counts to be of any value. Although only a few examples of this kind have been reported the hopeless prognosis has naturally served as a deterrent to those who would otherwise use the diones. However, I feel that in view of the large number of patients who have taken diones without ill-effect the dangers have perhaps been overemphasized. Often patients with *petit mal* may be treated with other drugs such as Diamox or amphetamine with a measure of success, and other mild cases frequently require no treatment at all, but when fits interfere with the education of a child or later with employment it may be essential to effect control with one of the dione group.

Some authorities (Lennox, 1945; Whitty, 1949; Symonds, 1950) have indicated that the suppression of *petit mal* with diones may provoke major seizures. My registrar has recently made a survey of 70 epileptics in whom EEG showed a rhythmic, bisynchronous, 3 per second, spike-and-wave abnormality. In over half of these, classical *petit mal* was associated with some other seizure pattern. These latter may either precede in time the onset of *petit mal* or alternatively follow after varying intervals and there would seem to be no statistical evidence for the belief that diones are responsible for the major fits that so often occur.

Conclusions.—Bromides should no longer play any part in the treatment of the epilepsies, being the least effective of all anti-convulsants and carrying a high toxicity rate, with lethal possibilities. The barbiturates are the least toxic of all anti-convulsant drugs and are still the first choice in the treatment of major, temporal lobe and other focal seizures. The hydantoins and primidone, alone or in combination, may succeed when the barbiturates have failed but they produce toxic reactions, though these are usually not serious if recognized early. The diones are perhaps the most valuable drugs in the treatment of *petit mal* but their toxic complications are serious and sometimes fatal and their use should probably be restricted to those patients having large numbers of minor attacks daily. Finally, it would seem that hæmatological changes of major or minor import are probably much commoner than has yet been suspected when using any of the modern anti-convulsants.

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Dr. David Stafford-Clark (York Clinic, Guy's Hospital):

Bromides.—In psychiatric practice most of the indications for which bromide is given—and these include states of acute grief and agitation on the one hand, and chronic disturbances of sleep rhythm on the other—are likely to be made worse rather than better, if the administration of this drug is continued for any length of time. This is particularly true when it is given to old people; and I would endorse a categorical veto on the exhibition of bromide to anyone over the age of 60, for any purpose whatever.

At the Maudsley Hospital we used to make serum bromide estimations as a routine on all patients admitted to the hospital, regarding a level above 200 mg.% as potentially toxic. Certainly, concentrations at and above this level can produce a state of confused drowsy irritability by day and disturbed paranoid and hallucinatory alarm and apprehension at night, in just those old people whose early senile dementing changes may have led to the administration of what was believed to be a safe and mild sedative over a period of several weeks.

Barbiturates.—Another stand-by whose use in psychiatry threatens to be equally abused is phenobarbitone. My own view is that there are only two really justifiable indications for phenobarbitone in psychiatric practice; the symptomatic alleviation of anxiety by small doses, regularly spaced; and the selected exhibition of a single 1 grain dose at 9 p.m. every evening for a month, as a trial therapeutic measure in the control of migraine, when this is allied to persistent emotional or environmental tension. It is only fair to add that this latter indication is borrowed from what was standard practice at the National Hospital, Queen's Square, when I was a registrar there.

All other occasions on which phenobarbitone is apt to be prescribed would probably be better met by an exhibition of other drugs. In particular, phenobarbitone should be rigorously avoided in all cases where there is an element of depression, since it undoubtedly tends to make depression worse, and can occasionally exacerbate it to the point of suicidal intensity. The dosage in anxiety states should not exceed ¼ grain t.d.s., and if phenobarbitone in this modest quantity is not sufficient to control symptoms, other drugs such as Sodium Amytal or Equanil should supplement or replace it. The practice of prescribing doses of ½ grain t.d.s. or even 1 grain b.d. in psychiatric conditions is in my view obsolete and essentially unprofitable.

Quick-acting barbiturates are of course extremely useful in psychiatric practice, and are

also reasonably safe, provided that they are not prescribed in undue bulk. Their chief toxic effects include:

(1) The risk of addiction, never to be overlooked, since addiction to barbiturate is by now probably the most common form of dependence on drugs in Western civilization.

(2) The additive effect when barbiturates are taken at the same time as alcohol; this has been suggested as a potentiating or synergistic effect, and has on occasion proved fatal when the dosage of barbiturate has not exceeded 9 grains of Sodium Amytal, and of alcohol, two large gins.

(3) Disturbance of glucose metabolism, both in the direction of hypo-and hyper-glycaemia, with a concomitant disturbance of vitamin B metabolism; both of which can be corrected by giving large doses of vitamin B when any barbiturates are prescribed for any length of time.

Amphetamine derivatives.—The wide use of Benzedrine, Dexedrine, and other amphetamine derivatives has made most of us familiar with the common clinical toxic effects which these very useful preparations can produce. They include anorexia of pathological degree, a tendency to hypertension, and once again the risk of addiction. This latter is perhaps less well recognized than the corresponding risk with barbiturates, but may not be much less common. One patient who was taking between 500–700 mg. of Dexedrine every day developed this addiction after being successfully weaned from alcohol, to which he had formerly been addicted, and put on to Dexedrine by his family doctor. Curiously enough, the only untoward symptom which this colossal dependence seemed to produce was a spontaneous tendency to fall asleep if he was without the drug for more than an hour or two.

However, there are other and far more ominous toxic effects which may be observed from time to time. Acute confusion and disorientation can occur when large doses of Dexedrine are combined with alcohol in purely social proportions; and Dr. P. H. Connell (1955) of the Maudsley Hospital has made some extremely interesting observations on acute psychotic episodes arising in the course of Dexedrine addiction and overdosage. Our own experience of toxic psychoses of this kind at Guy's has included 3 cases of acute paranoid delusions and hallucinations, with a marked strain of outright terror, and a constant urge on the part of the patient to escape from the delusional and hallucinatory pursuers. It is of some interest that 2 of these 3 cases were doctors' wives, and the third was a nursing sister. Psychotic reactions of this kind tend to settle down very rapidly once the drug is completely withdrawn, but produce sufficient disturbance during the withdrawal phase to require expert supervision, preferably in hospital.

The tranquillizers.—The number and complexity of drugs recently put on the market with the general object of producing varying degrees of subjective calmness, tranquillity, and detachment from sources of emotional stress, whether endogenous or exogenous, but without producing drowsiness or sedation in normal dosage, is legion. We have tried most of them in my Department, and while it would be invidious to mention those which appear to have no beneficial action whatever, and to produce in fact nothing but toxic side-effects, it may be helpful to mention some of the more generally useful preparations, whose toxic effects are usually avoidable provided effective supervision is maintained over dosage. These include:

(1) Largactil (chlorpromazine), Notensil (acetyl promazine), Sparine (promazine)—all phenothiazine derivatives.

(2) Rauwolfia, and associated alkaloids, including reserpine and *Rauwolfia serpentina.*

(3) Equanil (meprobamate) a propanol derivative.

(4) Frenquel and Meratran, two useful benzhydrol derivatives.

The first group of drugs are well known for their proven tranquillizing effects, particularly in states of excitement following withdrawal of other drugs; their clinical toxic effects include drowsiness, tachycardia and postural hypotension in moderate excess, with jaundice and Parkinsonism as more serious signs of overdosage or sensitivity. Less well-known complications can include an induced hypersensitivity to ultraviolet light, making sunbathing potentially dangerous in patients saturated with these drugs, and a lowering of the levels of vitamins B and C in the serum. This latter complication, like that attendant on barbiturate administration, can be prevented by concomitant administration of adequate vitamin supplements.

The toxic effects of the rauwolfia derivatives also include jaundice and Parkinsonism, the latter appearing relatively early; but the single most important clinical disadvantage is that drugs of this group are extremely depressing, and have certainly precipitated suicide in already depressed patients on more than one occasion. This complication can only be effectively avoided by careful selection of patients in the first instance, constant supervision

of response, and occasional concurrent administration of Ritalin, a piperidine derivative with a similar action to amphetamine preparations, but without their hypertensive effect.

Equanil is singularly free from toxic effects, although the possibility of blood dyscrasias in sensitive patients has been raised. I have never seen any; and in my own experience this drug, properly used, is without disadvantages.

Meratran has a similar effect to amphetamine compounds, but is certainly capable of increasing anxiety; it does not belong among the tranquillizers on its own account but is included because of its very close structural relationship with Frenquel. Frenquel is the gamma-isomer of Meratran and is of interest in being the first commercially available substance which can be used to block the hallucinatory effects of known hallucinogenic drugs, when given before their administration, or in some cases even when given afterwards. In the light of the theory put forward by Hoffer *et al.* (1954), the possibility that Frenquel might mitigate or control comparable symptoms of schizophrenia has held out hopes which remain as yet unfulfilled. No toxic effects have been reported from it.

Hallucinogens.—These include such substances as mescaline, lysergic acid diethylamide (L.S.D.), cannabis indica, and adrenochrome, and have been used chiefly in the investigation of the temporary psychoses, which can be induced by their administration. Two of these, cannabis indica and L.S.D., are currently in use as therapeutic agents; cannabis indica in some work we are doing at Guy's in the treatment of depersonalization, L.S.D. in some recent studies of the relief of chronic mental conditions at Powick Hospital. It is possible that all these drugs have in common a capacity to affect synaptic transmission throughout the central nervous system, but particularly in the cerebral cortex, and may produce their toxic effects by an extension of the physiological mechanism whereby adrenaline is presumed to produce changes in levels of awareness and interpretation of reality, by direct effect upon the brain.

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Dr. M. Weatherall (Department of Pharmacology, London Hospital Medical College):

I shall consider mainly some less well-known toxic effects of certain barbiturates, and the principal effects of the most recently introduced central depressants, the tranquillizers of various kinds. The relation between barbiturates and porphyria has often been put forward but never well supported, and it has been suggested that there is no connexion, or that barbiturates are capable of precipitating attacks in persons who were in any case porphyrics or that some cases of porphyria were a consequence of unusual sensitivity to barbiturates. Experiments in animals have generally yielded negative results, but recently Goldberg (1954) has shown that certain barbiturates are particularly potent in promoting the excretion of coproporphyrin and uroporphyrin in rabbits and that the chemical structure of the individual barbiturate is important in this context. Activity is much greater in barbiturates containing an allyl group, as in quinalbarbitone (Seconal) and allylisopropylbarbituric acid (Alurate), and still greater when two allyl groups are present, as in allobarbitone (Dial). This observation brings the effect into line with the porphyria which may be precipitated by the hypnotic Sedormid, also an allyl compound, but it does not lead to any correlation between activity on the nervous system and porphyrin metabolism, because allylisopropylacetamide is as potent as Sedormid and allobarbitone in disturbing porphyrin metabolism, but is devoid of hypnotic activity. The available evidence suggests that the excess porphyrin is produced in the liver and that the effect is in no way neurotoxic.

Another toxic effect, both of barbiturates and of most of the tranquillizers, is a drug rash. Skin eruptions of various kinds have been reported after chlorpromazine (Lehmann and Hanrahan, 1954; Lomas *et al.*, 1955), reserpine (Sariver-Foner, 1956), meprobamate (Selling, 1955; West and Fonseca, 1956), mephenesin (Wolf and Pinsky, 1954), and even methylpentynol (de Lamater, 1952). The incidence of such rashes is usually between 2 and

3%, and they commonly appear at the beginning of medication. It seems important to note that they have also been observed after administration of placebo tablets, containing such a pharmacologically innocent material as lactose. Thus Wolf and Pinsky (1954) treated 31 patients with various kinds of anxiety state alternately with lactose and mephenesin: the trial was a properly conducted double-blind in that neither physician nor patient knew when the dummy was being given, and it yielded three toxic reactions including an angioneurotic œdema and a skin rash, diagnosed as a characteristic dermatitis medicamentosa, both precipitated by the administration of lactose. The series is rather small, and more observations of this sort are most desirable, but it suggests that, particularly with the kind of patients to whom sedatives are commonly administered, caution is desirable in the interpretation of symptoms suggestive of a toxic origin. It does not, of course, mean that skin eruptions occurring after any of these drugs are never directly related to the drug administered, but it limits the value of estimates of the incidence of toxic effects, since they will be much affected by the kind of patient being treated. Just as the therapeutic value of a drug requires to be demonstrated by a blind therapeutic trial, unless the effect is very striking, so estimates of the incidence of toxic effects are liable to be misleading except when they are based on observations properly controlled by the administration of dummy tablets to a sufficient proportion of the group being treated.

All these reactions to barbiturates, however, make a very small contribution to the total loss of life caused by these drugs, which accounted for over 500 deaths in 1954 (Brooke, 1956) and perhaps ten times as many hospital admissions (Locket, 1956). Most of these deaths and intoxications were suicidal, but they were only possible because sufficient amounts of barbiturate had been made available on prescription to these patients. It seems impossible to assess whether all or any of these deaths would have occurred by other means if barbiturates had not been available to the persons concerned, but it is reasonable to suppose that the ease of this method of suicide contributed to the incidence, and to regard less liberal prescribing as desirable. In some of these cases, ethyl alcohol has been regarded as a contributory agent, and the term potentiation commonly appears. It is convenient to distinguish between potentiation and simple addition or summation of the actions of two drugs. If the dose of one drug necessary to produce a given effect is A, and the corresponding dose of another is B, and if the effect can be produced by a total dosage less than $\frac{1}{2}A+\frac{1}{2}B$, then potentiation has occurred; if the effect is just produced by $\frac{1}{2}A+\frac{1}{2}B$, the drugs are additive, and if more than $\frac{1}{2}A+\frac{1}{2}B$ is required, the drugs are to some extent antagonizing each other. Alcohol, like barbiturates, depresses the respiratory centre and in acute poisoning by any of these drugs death occurs from respiratory failure. There is no evidence that the agents either potentiate or antagonize each other, and half a lethal dose of alcohol and half a lethal dose of barbiturate are together lethal (Ramsey and Haag, 1946). Reported cases of death occurring after ordinary therapeutic doses or not greatly excessive doses of a barbiturate have generally been accompanied by very high concentrations of alcohol in the blood (Fisher *et al.*, 1948).

As alternatives to the barbiturates for some purposes there are the so-called tranquillizers of various kinds. Their appearance has coincided with much activity in studying the pharmacology and biochemistry of the central nervous system, and new facts are being discovered so rapidly that it is not easy to make a coherent picture about them. At present, the tranquillizers are a very unhomogeneous group of substances which differ in potency, and chemically, and pharmacologically. The most potent, and most complicated, are reserpine and chlorpromazine. Both, and particularly chlorpromazine, have a variety of dissimilar actions, mainly in the central nervous system. It is unusual for a drug to have fundamentally more than one or two actions, and this suggests that they act on some mechanism common to a variety of nervous pathways.

In the peripheral nervous system the synapses are particularly susceptible to the effects of drugs, and it is tempting to regard reserpine and chlorpromazine as drugs which modify transmission at central synapses of some kind. There is not much convincing evidence about the identity of central transmitters, but there are grounds for including acetylcholine, noradrenaline, and 5-hydroxytryptamine among the possible agents, as all these substances have characteristic localizations in the brain and show some fluctuations in concentration in relation to different physiological states. 5-hydroxytryptamine is particularly interesting because most of the hallucinogenic drugs, such as lysergic acid diethylamide, antagonize it, and reserpine liberates it from most of the sites in the body where it occurs. Some of the effects of reserpine may be due to the liberated 5-hydroxytryptamine, which can itself act as a central depressant, or to impaired function of the cells which have been depleted; but it is relevant that reserpine liberates other pharmacologically active bases from tissues as well. In the same way it is possible that chlorpromazine, and indeed all the antihistamines with central depressant effects, act on synapses where, perhaps, noradrenaline is the transmitting agent; but considerably more evidence is necessary than is at present available to justify such a hypothesis. From the point of view of toxic effects, the main dangers of chlor-

promazine lie outside the central nervous system, in causing jaundice and agranulocytosis, and there is little explanation of the way in which these events occur.

Of the milder tranquillizers, meprobamate (Miltown, Equanil, Mepavlon) and mephenesin (Myanesin) act by depressing polysynaptic reflexes (Berger, 1954) perhaps in a manner like but opposite to the effect of strychnine. There is no reason to relate their action to any known chemical transmitter. They are characterized by a very wide margin of safety, and there are individual reports of doses up to 40 grams in twenty-four hours being tolerated; so it does not appear that they affect any particularly vital mechanism.

Methylpentynol (Oblivon) is one of the higher alcohols, and its effects are much less specific and are closest to those of ethyl alcohol and the barbiturates. Probably it acts in the same way as ethyl alcohol, but it is more rapidly metabolized and small differences between it and ethanol in the rate at which the concentration rises and falls in different parts of the body may be responsible for the appearance of different symptoms. In view of its usually rapid inactivation it is curious that many of the toxic effects which have been described (May and Ebaugh, 1953; Marley and Chambers, 1956) have followed the intake of only moderately large doses (1–2 grams per day) for a few days. The symptoms are not very specific: Marley and Chambers describe nystagmus, diplopia, ptosis and muscular incoordination, and variation in mood, usually towards depression: the symptoms abate fairly rapidly on withdrawal of the drug. At the normal rate of inactivation, cumulation of methylpentynol would not be expected in these conditions, and estimations of its concentration in the blood when these symptoms occur would be useful in understanding how they arise.

The question arises as to whether harm may result from prolonged use of these drugs, particularly when they are self-administered. The matter has received considerable public attention because some of the tranquillizers have been, or are, freely available and are evidently being consumed somewhat indiscriminately. It is very difficult to decide what harm is accruing in this way. So far little direct physical damage has been reported, and the problem of control would be simpler if all the tranquillizers caused agranulocytosis as often as does amidopyrine: but the passage of time may bring more evidence of this sort. Some disturbances of behaviour have been reported, such as driving cars into buses, or motor cycles into walls or submitting to seduction by strangers (Pratap, 1956), but controlled studies are particularly lacking in these circumstances and it is very uncertain whether some of the events described would not have occurred without the intervention of a tranquillizer. On the face of the evidence behavioural disturbances are no worse than those produced by alcohol, and alcohol is almost certainly responsible for more road accidents than all the tranquillizers put together. And the possibility of dependence, habituation or addiction is an unassessed risk. Addiction has been reported, for instance, to meprobamate (Lemere, 1955) but mostly in patients who were receiving treatment for previous addiction to alcohol. The risk of addiction depends on the drug and the patient: the milder the central depressant action of the drug, the more important is the personality of the patient, and drugs which have no more powerful action than one of producing tranquillity are likely to be addictable only to a limited section of the community. Whether these risks taken together are great enough to make more stringent control appropriate remains a somewhat debatable question, but there is a good deal to be said against any encouragement of their wider consumption.

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BOOK REVIEWS

Schizophrenia 1677. A Psychiatric Study of an Illustrated Autobiographical Record of Demoniacal Possession. Psychiatric Monograph Series No. 2. By Ida Macalpine, M.D., and Richard A. Hunter, M.D., M.R.C.P., D.P.M. (Pp. ix+197; illustrated. £6 10s. Limited edition.) London: William Dawson & Sons Ltd. 1956.

Freud's explanation of paranoia was in some measure forced upon him, in that it had to be reconciled with the theoretical system he had already built up. He was well aware of the disability resulting from his neurological training and lack of mental hospital experience; and explicitly commented upon this himself. It was thus with enthusiasm that he analysed, in 1911, the autobiography of Daniel Paul Schreber, a sufferer from paranoid schizophrenia who made a remission good enough to permit him to write his own memoirs with insight and undisturbed by thought disorder. In 1923 a second opportunity presented itself when the autobiography of Christoph Haizmann came to his notice. Haizmann was a destitute painter who sold his soul to the Devil in the seventeenth century, and was clearly suffering from paranoid schizophrenia at the time of the sale. In addition to the patient's diary, we have nine paintings, and the statements of priests who observed his illness.

For a long time the Schreber memoirs were unavailable and in 1955 Macalpine and Hunter translated and published them. They have now, in the book under review, presented the full Haizmann manuscript which was written partly in Latin and partly in German, together with a translation and reproductions of Haizmann's paintings. The importance of these two very considerable achievements lies, as the authors stress, in the fact that Freud's theory of the paranoid states stems from his study of these memoirs. The theory has never been seriously challenged, partly because the Schreber analysis acquired too soon the immunity from criticism which belongs to a classic.

The authors have given in the book a fair and very readable summary of Freud's work—his investigation into the unconscious and the subsequent elaboration of a theoretical superstructure. With all the evidence before them, they have attempted to look through Freud's eyes and to demonstrate that the evidence in these memoirs did not justify the interpretation placed upon them. In this they have in your reviewer's opinion succeeded completely. Their views are summarized when they point out that the main objection to the Œdipus theory is that there is no indication in the memoirs that Haizmann was homosexual, and there is no mention at all of his father!

Chronic Illness in the United States. Volume II. Care of the Long-Term Patient. Prepared under the auspices of the Commission on Chronic Illness. (Pp. xiv+606. 68s.) Cambridge, Mass.: Harvard U.P. (for Commonwealth Fund). London: Oxford University Press. 1956.

A Commission on Chronic Illness was set up by the American Hospital Association, American Medical Association, American Public Health Association and the American Welfare Association to review all the problems relevant to chronic illness, and to advise on the means of integrating efforts to achieve their prevention and minimize disability. This book is the report of the Commission.

The first chapter deals with the patients and points out that "every long-term patient has one major need: to be looked upon as an individual, whole person". This unexceptional, if somewhat platitudinous statement is followed up by the recording and analysis of a large amount of relevant information. The broad issues in the care of long-term patients whether in their homes, those of others or in institutions or nursing homes, are supplemented by detailed enquiry into, for instance, the dental care of these patients, or the effect of poor housing on their condition. Anong the many interesting facts which emerge is the economic aspect of rehabilitation and the very great saving in cost which results from it.

The Commission conclude that most long-term patients are best cared for in their own homes, and this no one would dispute.

It appears, however, that there are in the United States, as in this country, deficiencies in the various services which are required if this is to be done satisfactorily. In fact, throughout the whole report there is a clear parallel between our difficulties and theirs, and thus a study of this book will repay those interested in the most pressing problem of the care of the chronic sick.

The Social Problem of Mental Deficiency. By N. O'Connor, M.A., Ph.D., and J. Tizard, M.A., B.Litt., Ph.D. (Pp. viii+182; illustrated with a number of diagrams. 30s.) London and New York: Pergamon Press. 1956.

This book is inspiring in its optimism about mental defectives who only too frequently are regarded as beyond human aid. The authors have set out the experiments which guided them in formulating successful principles of training and the book should be read by all those responsible for the care and after-care of mental defectives. They have criticized many legends about defectives which tend to be perpetuated in successive editions of textbooks.

Thus, while half the adults certified as being feebleminded in Greater London have intelligence quotients of more than 70, the authors point out that their social incompetence derives from deficiencies amenable to training—occupational ineptitude, illiteracy, and bad behaviour. Neurotic traits in defectives have been found to be treatable and to improve with increasing years. The great majority of educationally subnormal school leavers can take their places with other adolescents at the work bench and at the counter, and large numbers of imbeciles can work in sheltered workshops. Finally, the authors note, the correlation between defect and delinquency has been over-exaggerated.

Some very useful criticisms are made of the type of training in mental deficiency colonies. Too much training is devoted to the filling in of time without consideration of the usefulness of the work done; and too much use is made of obsolete equipment. Defectives, like the rest of us, need incentives to work, and in particular they should be paid, and learn to use money. Much closer contact with industry is required. The whole question of the comprehensive colony as opposed to specialization on the London principle is considered. The authors state the arguments for and against the comprehensive colony. Many will not agree with their conclusions and indeed your reviewer does not, but the discussion is most interesting. This admirable book ends with a plea for further research, more extensive community services, and a revision of the law.

The Practice of Medicine. Edited by Jonathan Campbell Meakins, C.B.E., M.D., LL.D., D.Sc. 6th edition. (Pp. 1916; illustrated. £6.) London: Henry Kimpton. St. Louis, U.S.A.: The C.V. Mosby Co. 1956.

This edition of Meakins' textbook of "The Practice of Medicine" has now over 80 contributors and the Editor has delegated responsibility to a number of associate editors who, in their turn, have invited specialists in their subjects to contribute to the various sections.

The disadvantage of so many contributors (preponderantly American) to special sections is the risk of re-duplication. It is, however, true to say that the associate editors have succeeded in the main in producing an integrated and co-ordinated work. On the whole the anatomical, physiological, pathological, emotional and environmental factors have received due recognition throughout the text. There is an excellent chapter under "The Allergic States" on the systemic collagen diseases, and one feels that polyarteritis nodosa would be better placed in this section than under "Diseases of the Blood Vessels". The section on chemotherapy is good. It seems a pity, however, that Aureomycin and Terramycin, for example, should not be given under their pharmacopœial names.

The sections on diseases of the respiratory and cardiovascular systems are on the whole comprehensive but the significance of the pneumoconioses merits more space than is accorded to it in this section. By way of contrast one is pleased to note the attention accorded to "the psychosomatic aspects of medicine" in a special section.

The limited but useful number of references at the end of each section is to be commended.

The illustrations throughout the book are excellent and the book is beautifully produced. It can be strongly recommended to the student of medicine.

Medical Guide to Vocations. By René Biot, M.D., and Pierre Galimard, M.D. Translated and adapted by Robert P. Odenwald, M.D. (Pp. xx+303; 18s.) London: Burns & Oates. 1955.

The word "Vocations" in this title is used in the strict sense of the "call" to the religious life. The authors tabulate the principal hereditary factors and temperamental constitutions which are medical contra-indications to admission to the seminary or the novitiate. Paranoia, hypochondriasis, hysteria, cyclothymia and schizoid and emotional reactions are described, and the difficulties in practising chastity are very fully considered. In the second half, devoted to the "Years of Formation", such problems as asceticism, hygiene, dispensation from vows and obligations, and readaptation to lay life for those who have to be rejected, are sympathetically discussed. There is a good deal of repetition, but the book may be recommended to any practitioner invited to assume the medical care of those intended for the priesthood or conventual life. The translation is excellent.

Section of Pathology

President—Professor JOHN W. S. BLACKLOCK, M.D.

[*March* 19, 1957]

Some Observations on the Effect of Fats on Blood Clotting

By J. D. BILLIMORIA, EUNICE LOCKEY and N. F. MACLAGAN

Department of Chemical Pathology, Westminster Medical School, London

THE effect of lipids on blood coagulation has recently become of great interest in relation to the theories of the pathogenesis of coronary atheroma. The early observations of Macfarlane, Trevan and Attwood (1941) and Fullerton and Anastopulos (1949) that certain samples of lecithin were accelerators of blood clotting were followed up by Robinson and Poole (1956), who showed that chylomicra from rat chyle accelerated the clotting of rat plasma and that pure phosphatidyl ethanolamine (P.E.) showed a similar effect. The effect of the chylomicra was attributed to their P.E. content.

The possible importance of dietary fat has also been recognized, but until recently little attention was paid to the nature of the fat in fatty foods, and the general impression existed that the total dietary fat was the most important figure for study. Thus many workers have reported the results of feeding fatty meals to human subjects and while Waldron, Beidelman and Duncan (1951), Fullerton, Davie and Anastopulos (1953), O'Brien (1956), Hall (1956) and Buzina and Keys (1956) have produced shortening of clotting times in this way, others have failed to recognize these changes either with certain techniques or after feeding certain fats (Tulloch, Overman and Wright, 1951; Manning and Walford, 1954). In our own work butter gave positive and margarine gave negative results (Maclagan and Billimoria, 1956). We feel that at least some of these discrepancies may depend on minor but important points of technique considered in the first section of this paper, and also upon the nature of the fats fed.

METHODS

Russell viper venom (*Stypven*) *clotting times.*—This is a particularly convenient technique to use since the Stypven is fat free and can be made to give very reproducible clotting times on single plasma specimens. However, a number of factors influence the results significantly, such as the initial treatment of blood, the ionic strength, the concentrations of calcium and venom, the presence of phenol in the solvent supplied by the makers, and the order of addition of the reagents. We have made a special study of the influence of these factors on the sensitivity of the system to added fat. It was established that optimum conditions include the use of platelet-poor plasma under isotonic conditions, the venom and M/30 $CaCl_2$ solution being added simultaneously as a mixture. The presence of phenol was undesirable as it produced a considerable shortening of the clotting times which was greater for fasting than for lipæmic plasma. Similar effects were produced by a delay between the addition of venom and $CaCl_2$, which therefore also reduced the effects of added fat. This difference between the delayed and instantaneous times suggests that venom interacts with some plasma component before the addition of calcium. The use of platelet-poor plasma was not so essential as, contrary to the previous suggestions in the literature, we obtained good reduction of clotting times by the addition of fat to platelet-rich plasma. The former is, however, preferable as it is more stable and the results obtained with it are more reproducible.

Recalcification methods.—Experiments with snake venom have the disadvantage of introducing a non-physiological thromboplastin so that we felt the need for other techniques and have found that the recalcification of plasma and of whole blood can be used to demonstrate the effect of an active fat. Here again it is important to use the optimum calcium concentrations and to maintain isotonic conditions.

The three techniques finally adopted were as follows:

Reagents.—

(1) *Venom-$CaCl_2$*
One ampoule of Stypven (0·5 mg.) dissolved in 5 ml. 0·1 M NaCl, 5 ml. M/30 $CaCl_2$ added.

(2) "Normal" saline (0·9% NaCl).

(3) $CaCl_2$—saline (*a*) 1 vol. M/30 $CaCl_2$.
1 vol. 0·2 M NaCl.
(*b*) 1 vol. M/15 $CaCl_2$.
1 vol. 0·1 M NaCl.

Procedure.—Blood is collected in a nylon syringe with siliconed needle into 1/9 vol. of 3·8% sodium citrate and centrifuged at 4,000 r.p.m. (2,900 *g*) for ten minutes. Plasma is stored in individual silicone tubes. Clotting is carried out in glass tubes at 37° C.

Venom	Plasma	Whole blood (citrated)
0·1 ml. plasma	0·1 ml. plasma	0·2 ml. blood
0·1 ml. saline (2)	0·1 ml. saline (2)	0·1 ml. saline (2)
0·2 ml. venom-$CaCl_2$	0·2 ml. $CaCl_2$/saline (3*a*)	0·1 ml. $CaCl_2$/saline (3*b*)

With these techniques normal fasting plasma gives the following approximate values:

Stypven time	30 to 35 seconds
Plasma recalcification	3 to 4 minutes
Whole blood recalcification ..	2 to 3 minutes

In Vitro Tests

The effects of a number of foodstuffs on blood clotting have been studied *in vitro* by those three techniques. As previously reported, only those foods containing milk fat gave strongly positive results, other fatty foods being relatively inactive. Two fatty foods, butter and margarine, were studied in some detail. It was shown with the venom technique that at optimum concentrations butter caused an 80% shortening of clotting time as compared with only 18% by margarine. Similar effects were obtained in the recalcification of plasma and of whole blood, although the percentage changes in clotting times were somewhat smaller. At very high concentrations of fat the acceleration of clotting was somewhat diminished particularly in the recalcification technique; this inhibition is provisionally attributed to mechanical interference of excess fat but is being further studied.

With the venom procedure, 10 mg. of butter per system gave a maximum shortening effect, with clotting times of 6–8 seconds. The unit of clotting activity is defined as the amount of food required to produce the same effect as that produced by 10 mg. butter, hence butter contains 100 units/gram. On this basis arbitrary units have been assigned to other foods (Maclagan and Billimoria, 1956). With less active foods, which fail to produce clotting times as low as 8 seconds, the units are calculated from a butter dilution curve so that, for example, margarine contains about 1 unit per gram.

Preparation of Active Principle from Butter

In the course of work on the isolation of the active principle from butter, during which all procedures were followed by an estimation of clotting activity as indicated above, it was found that the activity was attached to protein, and hence on centrifuging warm butter the inactive neutral fats could be easily removed. This enabled us to work with quantities of 50–100 lb. of butter at a time. The active lipoprotein was broken down with hot acetone and the activity transferred with dry chloroform on to a silicic acid column. Graded elution with methanol in chloroform yielded the most active fraction at a concentration of 8% methanol.

The phospholipid had an activity of 200 units per mg. representing a 2,000-fold concentration of the original butter. It was also active in the thrombin generation and thromboplastin generation tests. The substance is much more active than a synthetic specimen of L-dimyristoyl-phosphatidyl-ethanolamine (kindly supplied by Dr. E. Baer, University of Toronto, Canada), which gave negligible shortening of venom time with fasting human plasma. Our preparation, which is not identical with the P.E. tested by Robinson and Poole (1956), had an N : P ratio of approximately unity but contained no free amino N. Mild acid hydrolysis yielded galactose, ethanolamine and serine, and converted all the N to the amino form, suggesting an N glycoside linkage. The chemical constitution is under further investigation.

A fuller account of this work will be published elsewhere. We are much indebted to Dr. J. G. Humble, M.V.O., for advice and criticism. The work was supported by generous grants from the Endowment Funds of Westminster Hospital.

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Dr. B. W. Lacey asked if colostrum fat had been tried as a source of clotting factor and if the action of the clotting factor was influenced by the level of cholesterol.

Professor N. F. Maclagan in reply: We have not tried colostrum fat. So far as we know, the plasma cholesterol does not affect clotting systems directly.

Staphylococcal Antibody in Osteomyelitis and Suppurative Arthritis

By CHARLES H. LACK

Institute of Orthopædics, Royal National Orthopædic Hospital, London

SEROLOGICAL tests for the diagnosis of staphylococcal infection are of poor repute. Nevertheless recent experience has led me to the conviction that an examination of the blood for staphylococcal antibody should be carried out more frequently for the diagnosis of unexplained pyrexias and for bone and joint disease.

Table I lists the commoner antigens of pathogenic staphylococci which have been characterized; the percentages are approximations and are based on published figures.

TABLE I.—DISTRIBUTION OF STAPHYLOCOCCAL ANTIGENS

Antigen	Produced by approx. %
Coagulase	100
Alpha-hæmolysin	80–100
Delta-hæmolysin	97
Panton-Valentine leucocidin ..	50
Hyaluronidase	95
Staphylokinase	90

If coagulase is produced by all pathogenic strains then the titration of anti-coagulase would appear to be the obvious choice, but this is impracticable at present. There appear to be at least three antigenically-distinct coagulases, and we wait on the provision of purer coagulase preparations as well as on purer fibrinogen substrate. Alpha-hæmolysin is the only staphylococcal antigen available as a standardized commercial preparation; its antibody is the one I have been measuring. Though delta-hæmolysin and hyaluronidase have almost as universal a distribution as coagulase, they are poor antigens. Interest in the Panton-Valentine leucocidin has recently been revived by Gladstone and van Heyningen (1957). I am not aware of any reports on anti-staphylokinase.

To return to the measurement of anti-alpha-hæmolysin, this is one of the simplest of serological tests and can be performed by a technician in an hour and a half. The patient's serum is inactivated by holding at 56° C. for 30 minutes. Dilutions of serum are made in 0·5 ml. volumes of saline. To each dilution of serum is added one unit of standard toxin in 0·5 ml. of saline +0·1% gelatin. The toxin is prepared from the Lyophilized Staphylococcal Alpha Hæmolysin of the Wellcome Research Laboratories. After 30 minutes standing at room temperature, 0·1 ml. of a 10% suspension of fresh rabbit cells is added to all tubes, including two controls—one serum alone and one toxin alone. All tubes are incubated for an hour and the end-point of inhibition by anti-toxin is determined by the tube showing 50% hæmolysis. As one unit of toxin has been placed in each tube, the titre of

antihæmolysin is the denominator of the dilution fraction. Most workers agree that the majority of healthy people have titres of less than 2 units.

Table II shows the distribution of antibody levels among patients at the Royal National Orthopædic Hospital; and Table III the totals of patients with raised titres expressed as

TABLE II.—ANTI-ALPHA-HÆMOLYSIN TITRES OF HOSPITAL PATIENTS

	Osteomyelitis	Secondary staph. infection	Presumed staph. infection	No staph. infection
Less than 2 units/ml. ..	33	20	—	231
2–4 units/ml.	21	11	—	13
4–8 units/ml.	10	10	1	1
8–16 units/ml.	5	2	1	—
16–32 units/ml.	5	3	2	—
Total 369	74	46	4	245

TABLE III.—PERCENTAGE OF PATIENTS WITH TITRES OF 2 UNITS OR OVER OF ANTI-ALPHA-HÆMOLYSIN

	%
No staph. infection	5·7
Staph. osteomyelitis and suppurative arthritis ..	55·4
Staph. infection elsewhere	56·5

percentages. It may be true that higher levels of antibody are encountered more frequently in patients with osteomyelitis, but in this series a patient with staphylococcal pyelonephritis had as high a titre as any patient with osteomyelitis, and the highest titre I have seen recorded (Bergquist, 1950) was that of a patient who developed staphylococcal empyema and whose titre rose from a pre-infection level of 1 unit to 440 units within a month.

The fact that about 45% of patients known to have staphylococcal infection, whether osteomyelitis or otherwise, have titres of less than 2 units would seem at first to make this test of very little value. On the other hand, we have found that a high titre, and more especially a progressively rising titre, is of the greatest help on occasions, as in the following cases.

Case I, a girl, and *Case II*, a boy, both aged 14. Each first complained of pain in the right side, the girl for eleven weeks and the boy for eight weeks. Both were diagnosed as having appendicitis, but appendicectomy did not cure the pain. In both cases the diagnosis was then changed to tuberculosis of the spine on radiological grounds. The girl was put on a course of anti-tuberculosis therapy. Both were eventually transferred to our hospital. Fig. 1 shows our findings with respect to the girl.

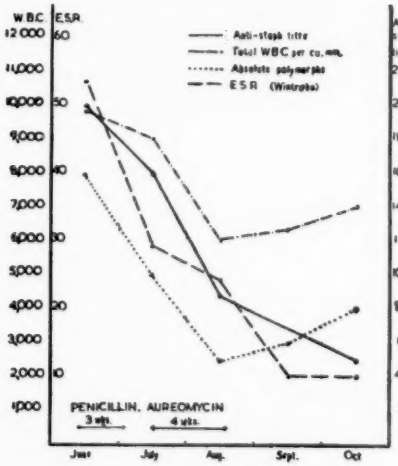


FIG. 1 (*Case I*).

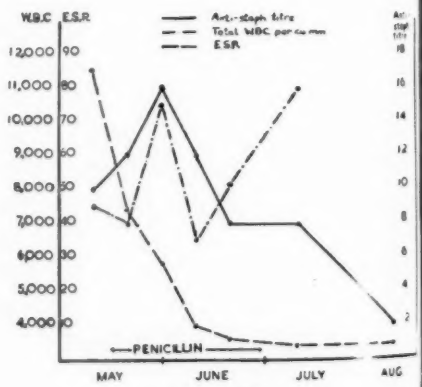


FIG. 2 (*Case II*).

On admission she was found to have 20 units of staphylococcal antibody and straight away was given penicillin. After three weeks this was changed to Aureomycin, which was continued for four weeks. By the time she was discharged her titre had fallen to 4 units.

The boy, who came to us twelve weeks after the onset of his pain and two weeks after his appendicectomy, had a titre of 10 units on admission (Fig. 2), which continued to rise for a time, while receiving penicillin, and then came down to 2 units. His total leucocyte count was even lower than the girl's, being only 7,500 per c.mm. and the absence of leucocytosis made some clinicians doubt whether this could be a staphylococcal infection.

Case III.—Woman, aged 58, developed pain radiating down the back of her right leg following a fall in December 1954. In March 1955 there was a sudden exacerbation of pain and she was admitted with a diagnosis of chronic back strain. Her antibody titre on admission was found to be 20 units, sedimentation rate 50, and leucocyte count 6,050 (Fig. 3). X-ray showed gross narrowing

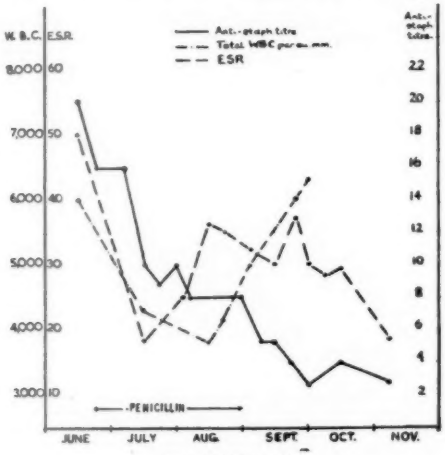


FIG. 3 (*Case III*).

of the I.V. space 4/5 and erosion of the L.V.4 anteriorly. Her antibody titre fell steadily on penicillin until, at her discharge on October 18, it was 4 units and her sedimentation rate 27 mm. in one hour (Westergren). She was then free from pain and X-ray showed that her lumbar vertebræ were fusing. A month later her antibody titre was 3 units, sedimentation rate 18 mm. and she was in excellent health. There was satisfactory consolidation of her lumbar vertebræ with no deformity.

Case IV.—A woman of 49 developed bronchitis and pleurisy at the end of October 1954. She spent fifteen days in bed and was given sulphonamide tablets. She then developed pain in the middle of her back at the level of the tip of her scapula, particularly noticeable at night. X-ray showed a destructive lesion of D.11, with loss of disc space, and the patient was admitted with a provisional diagnosis of spinal tuberculosis. On admission her only abnormal sign was tenderness over L.1 and 2, her temperature was normal and her white cell count was 17,800. Sedimentation rate 13 mm. in one hour (Westergren). Mantoux positive. Her anti-alpha-hæmolysin titre was 4–5 units. She was given penicillin and her titre fell to 3 units and her total white count to 8,000. She was discharged in good health.

This serological test has been of value in correcting the diagnosis in a variety of disorders, the most common being an early spinal lesion that has been labelled tuberculous. It has also given a clue to the cause of the fever of several patients who have been treated with cortisone for rheumatoid arthritis or lupus erythematosus and who have subsequently developed "silent" staphylococcal abscesses. In cases such as spinal disease, the results consequent on the use of this test have been highly gratifying—the patients have been cured much sooner than they would have been had they remained on their anti-tuberculous regimen. But why do only half of the patients with staphylococcal infection show this response. Is it due to lack of antigenic stimulus? By all accounts at least 80% of pathogenic strains of *Staph. pyogenes* produce alpha-hæmolysin *in vitro*. Incapacity to produce antibody is not likely to be an explanation, as the giving of toxoid to low-titre patients with staphylococcal infection has always produced a rise in antibody. The walling-off of the antigen may explain low titres in chronic cases, and we have examples of rise in antibody following operative interference, but this does not account for low antibody levels in early and progressive infections. Duration of infection cannot explain the discrepancy. We have the record of a patient whose titre rose to 8 units within three weeks of the onset of osteomyelitis. From Table IV it may be seen that the time factor does not appear to be very important.

TABLE IV.—ANTI-ALPHA-HÆMOLYSIN AND ANTI-LEUCOCIDIN TITRES OF PATIENTS WITH STAPHYLOCOCCAL OSTEOMYELITIS

Case	Duration	Anti-alpha	Anti-P.V.L.
1	3 weeks	8	80
2	1 month	10	200
3	1 month	2	12
		2–4	100
		2	40
4	6 weeks	Operation—2	Not tested
		2	100
		4	80
5	7 months	16–20	100
		10–16	80
6	7 months	8–10	16
		4–8	16
		2–4	24
7	10 years	Operation— 2	16
		2–4	24
8	37 years	2	16–20

I shall refer briefly to another antibody, anti-leucocidin (Anti-P.V.L.). The normal level in serum seems to be up to 10 units. Gladstone has been measuring the anti-leucocidin titres in the sera of some of our patients and, so far, it appears that this may be a more sensitive indicator of staphylococcal infection in some cases. Table IV sets out for comparison the two levels in a few patients. In Cases III and IV the anti-leucocidin titre was a better guide, but in Case VI the anti-alpha-hæmolysin titres were more helpful. At present it seems worth while to carry out both tests.

I would like to thank Dr. Gladstone for allowing me to quote his findings.

REFERENCES

BERGQUIST, S. (1950) *Acta med. scand.*, **136**, 343.
GLADSTONE, G. P., and HEYNINGEN, W. E. VAN (1957) *Brit. J. exp. Path.*, **38**, 123.

Dr. E. S. Duthie said that numerous measurements made by him on the antibody level against staphylococcal coagulase in the sera of normal individuals showed a wide variation. Similar results were found in 1950 by Rammelkamp, Hezebicks and Dingle in America and for this reason it was unlikely that the level of antibody against coagulase would be of value in the diagnosis of staphylococcal infections. On the other hand he had found high anti-alpha-lysin levels similar to those given by Dr. Lack in staphylococcal bone infections. Since the level of anti-alpha-lysin was relatively constant in normal cases he felt sure that this was a most valuable test and it would be interesting if at the same time anti-leucocidin values could be measured.

REFERENCE

RAMMELKAMP, C. H., HEZEBICKS, M. M., and DINGLE, J. H. (1950) *J. exp. Med.*, **91**, 295.

Dr. Herta Schwabacher said that she had found the estimation of anti-alpha-hæmolysin to be of diagnostic value only when the focus of staphylococcal infection was in muscle or bone. She asked whether Dr. Lack had ever found a significant titre of staphylococcal antibody in staphylococcal skin infections? With the co-operation of Mr. H. F. Lunn, Casualty Officer, Peace Memorial Hospital, Watford, she had examined the sera in a small series of patients with furunculosis. On no occasion was antibody detected. These patients were given a course of staphylococcal toxoid and their sera when retested failed to show any rise in titre.

Dr. Lack in his reply stated that he too had never observed staphylococcal antibody in infections of the skin, but had done so when these patients had received toxoid therapy.

Dr. K. B. Rogers asked Dr. Lack whether his work would suggest that staphylococcal antitoxin would help in the treatment of extremely ill, toxic, cases of acute osteomyelitis as in the last few years two children with staphylococcal osteomyelitis had been lost, although the staphylococci from both cases were fully sensitive to penicillin.

Dr. Lack said that he had had no experience in the use of anti-toxin for the treatment of the toxæmia of acute osteomyelitis in children.

Dr. B. W. Lacey said that the cases mentioned by Dr. Rogers would seem to be ideal for the combined use of steroid and chemotherapy.

Section of Surgery

President—ERIC A. CROOK, M.A., M.Ch., F.R.C.S.

[*May* 1, 1957]

DISCUSSION ON CHRONIC RELAPSING PANCREATITIS

Dr. Henry Doubilet (New York):

Physiological Basis of Treatment of Pancreatitis

The anatomical and physiological conclusions, resulting from experience with 500 cases, upon which the treatment of pancreatitis by sphincterotomy is based may be summarized as follows:

Neither the gall-bladder, biliary tract nor pancreas can be considered in therapy as an isolated organ subject to accidental disease. They form part of the biliary-pancreatic-duodenal system which functions physiologically as a unit for the production of digestive juices and for the digestion of food. Dysfunction or disease of any part of this system may affect the other organs or be the cause of their inflammation.

A common passageway exists in all cases of recurrent pancreatitis. This means that when the sphincter of Oddi becomes spastic, a portion of the bile may be diverted into the pancreatic duct. This common passageway can be demonstrated to be present functionally in the living patient at operation, or post-operatively, by injecting a radiopaque solution into the biliary tract after deliberately producing spasm of the sphincter of Oddi by intraduodenal instillation of N/10 HCl. A typical cholangiogram is produced with visualization of the pancreatic duct by reflux (Fig. 1). The common passageway can also be demonstrated by direct observation at operation or by reflux studies when a T-tube is present in the choledochus.

The key to the ætiology of inflammatory disease of the biliary-pancreatic duct system is the sphincter of Oddi. Increase in its tonus (or spasm) is produced primarily by frustrating emotional disturbances, exhaustion, or pain in other parts of the body (Fig. 2).

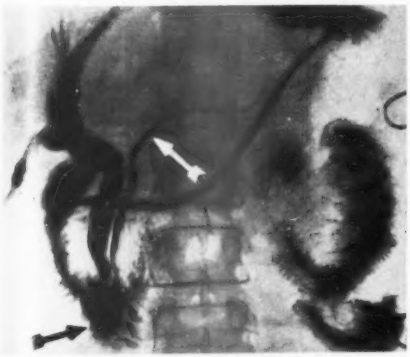


FIG. 1.—Operative cholangiogram demonstrating common passageway. While the radiopaque solution was being injected, spasm of the sphincter of Oddi was produced by the injection of N/10 hydrochloric acid through a Rehfuss tube, whose metal tip was positioned against the papilla (black arrow). The consequent reflux resulted in visualization of the whole duct of Wirsung (white arrow).

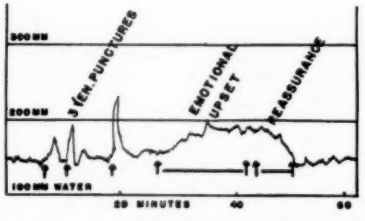


FIG. 2.—Kymographic record of the tonus of the human sphincter of Oddi showing its reaction to pain and to emotion.

The entrance, under tension, of a concentrated solution of bile salts into the pancreatic duct produces an acute inflammation varying in degree from mild œdema to fulminating hæmorrhagic necrotizing pancreatitis. It follows therefore that once pancreatitis is established a normal gall-bladder with its great ability to concentrate bile becomes a liability and should be removed. If the gall-bladder is diseased, pain due to obstruction produced by calculi in the gall-bladder, or in the common duct after their passage into the biliary

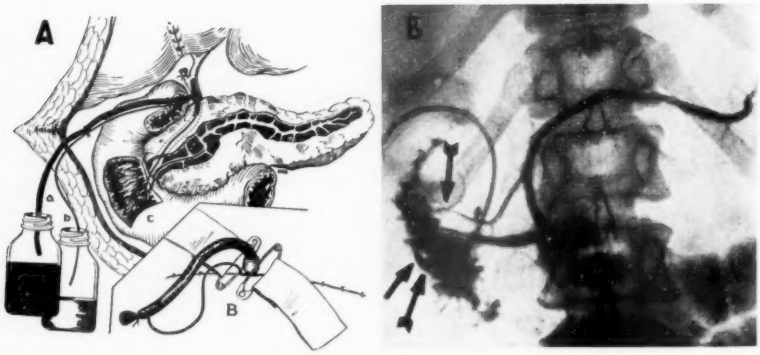


FIG. 3A and B.—Pancreatography is accomplished by inserting a plastic tube into the duct of Wirsung following sphincterotomy as illustrated in A. The tube (*b*) passes alongside the T-tube (*a*) through the cut sphincter of Oddi and up the pancreatic duct. Bile and pancreatic juice are collected separately. After four days the T-tube is tied and the polyvinyl tube inserted into it by means of a needle (insert B), allowing pancreatic juice to circulate back into the duodenum. Fig. 3B shows a typical pancreatogram; the plastic tube is shown passing down the common duct, making it circle in the duodenum (2 arrows), and passing up the duct of Wirsung. The accessory duct (one arrow) is also visualized. The radiopaque solution is contained by the ducts and does not seep into the acinar tissue.

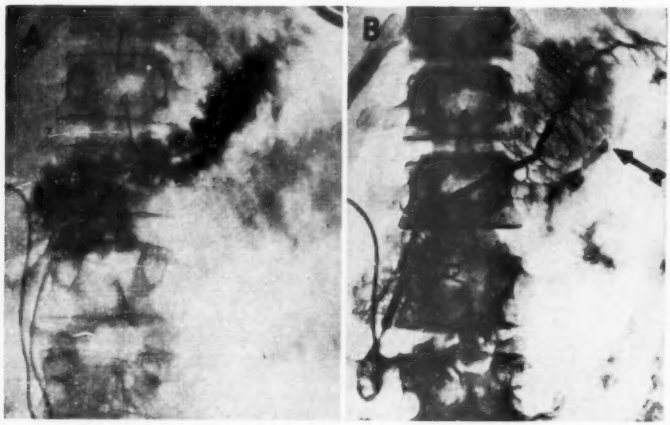


FIG. 4.—Resolution of inflammation of pancreas. An operative pancreatogram (A), demonstrated the whole pancreas due to the presence of acute inflammation and œdema. The permeability of the duct epithelium allowed the radiopaque solution to permeate the acinar tissue. Two weeks later, a pancreatographic study showed almost complete resolution of the acute process. Only a small area near the tail (arrow) was partly opaque.

tract may produce reflex spasm of the sphincter of Oddi. Depending on the anatomical relationship of the two duct systems, and on the relative variability of their pressures, bile may then enter the pancreas and produce a pancreatitis.

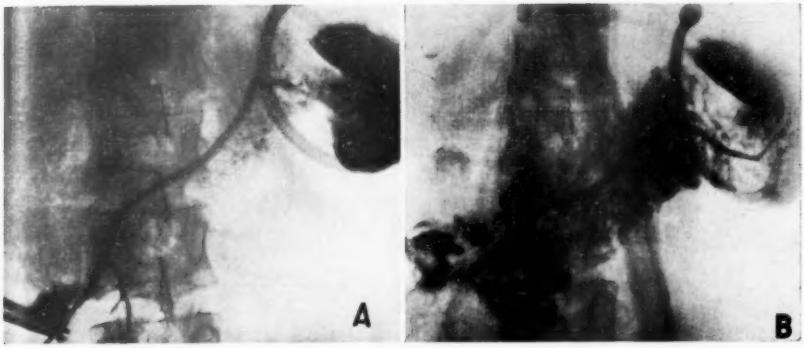


FIG. 5.—Deliberate injection of the pancreas. An operative pancreatogram (A) showed the pancreatic duct. After waiting 10 minutes for the inflammatory response to the radiopaque solution to develop, more solution was injected. Due to the resulting permeability of the duct epithelium, the whole pancreas was outlined. This radiographic technique can be used in the search for a tumour of the pancreas.

The maximum pressure of bile secretion by the liver is 300–400 ml. of water. The force of contraction of the gall-bladder is approximately 250 ml. The secretory pressure of the pancreas is also between 300 to 400 ml. However, although the liver secretes continuously, the pancreas secretes only in response to food so that there are periods when it is possible for bile to enter the pancreatic duct when the sphincter of Oddi is in spasm. Acute inflammation results in permeability of the duct epithelium so that pancreatic juice can be reabsorbed through the walls of the ducts into the tissues. This is exemplified in pancreatographic studies. A technique has been developed for intubation of the pancreatic duct (Fig. 3A). By such means not only can operative pancreatograms be made, but the subsequent course of inflammation can be followed by serial pancreatograms. Normally, in the absence of inflammation, the radiopaque solution is contained by the duct epithelium (Fig. 3B). In the presence of acute inflammation, the radiopaque solution permeates the epithelial wall and renders the whole pancreas opaque. With resolution of inflammation this opacity of the pancreatic tissue no longer occurs (Figs. 4A and B). The reverse can also be produced deliberately. The concentrated radiopaque solution tends to be irritating and, within a period of a few minutes, produces an inflammatory reaction. Injection of more radiopaque solution 10 minutes later results in the whole pancreas becoming opaque (Figs. 5A and B). High pressure within the pancreatic duct system also leads to increased permeability of the duct wall. Sphincterotomy, by lowering the pancreatic intraductal pressure, will reverse the process and help in the resolution of the acute inflammation.

The pain in pancreatitis is due to two causes: (*a*) Distension of the bile and pancreatic ducts behind a spastic sphincter. The spasm, and therefore the pain, may be intermittent or persistent. This pain is permanently abolished by sphincterotomy. (*b*) The acute chemical inflammation resulting from reflux of bile into the pancreatic duct involves the parietal peritoneum and the retroperitoneal tissues. Sphincterotomy will prevent these periodic episodes of reflux of bile into the pancreatic duct and thus abolish the pain produced by the acute inflammation.

There is no evidence that obstruction of the pancreatic duct plays a part in the origin of pancreatitis. On the contrary, the pancreatic duct is usually dilated and even sacculated in cases of long-standing pancreatitis as a result of prolonged spasm of the sphincter of Oddi (Fig. 6). The term "spasm" does not carry any connotation of obstruction. It



FIG. 6.—Dilatation of the bile and pancreatic ducts as a result of long-standing spasm of the sphincter of Oddi. This patient had a 20-year history of recurrent attacks of severe pancreatitis. The gall-bladder was normal, and the common duct was clear of stones. An operative cholangiogram revealed a dilated common duct (white arrow) and a sacculated enlarged pancreatic duct (black arrow).

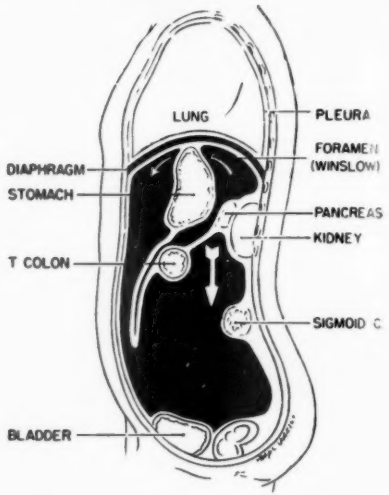


FIG. 7.—Spread of activated exudate during attack of acute pancreatitis. Diagrammatic sagittal section through the left nipple line shows (*a*) intraperitoneal spread through foramen of Winslow (curved arrow) and through the base of mesocolon (straight arrow), and (*b*) retroperitoneal spread around kidney, down to the sigmoid mesocolon, anteriorly between leaves of mesocolon, upwards to diaphragm and along aorta to the posterior mediastinum.

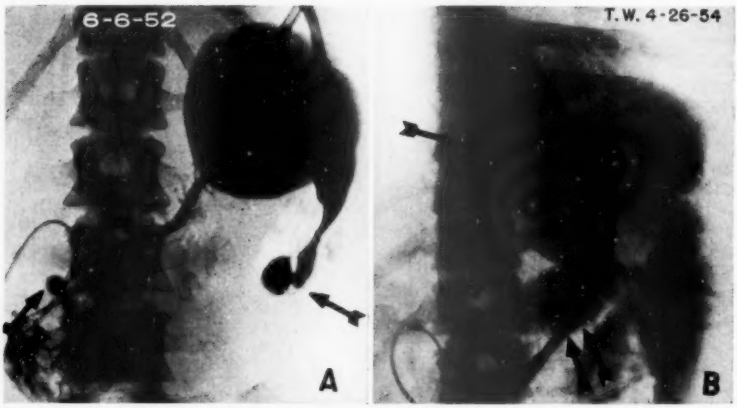


FIG. 8.—Examples of pseudocyst formation due to retroperitoneal spread of exudate and pancreatic juice. Pancreatographic studies showed a large pseudocyst (A) beneath the left diaphragm with extension down to the sigmoid mesocolon (arrow), and (B) a huge pseudocyst in the posterior mediastinum (arrow), extending to the 6th thoracic vertebra. Note (2 arrows) opacification of the pancreas due to residual inflammation. These pseudocysts resolved completely after drainage through the plastic tube inserted into the pancreatic duct through the sectioned sphincter.

means that the bile and pancreatic juice flow into the duodenum against increased resistance.

The pancreas is a retroperitoneal organ, so that rupture of any of the smaller ducts during a phase of necrosis will enable pancreatic juice to enter the retroperitoneal space. Increased intraductal pressure as a result of sphincter spasm will divert pancreatic juice into this space and result in the rapid formation of pseudocysts (Fig. 7). The pancreatic juice may dissect downwards as far as the sigmoid mesocolon on the left, upwards towards the diaphragm (Fig. 8A), and even into the posterior mediastinum along the aorta to form a pseudocyst in this thoracic space (Fig. 8B). Sphincterotomy will reduce the intraductal pressure and lead to the disappearance of these pseudocysts (Figs. 9 A–D). If a pseudocyst

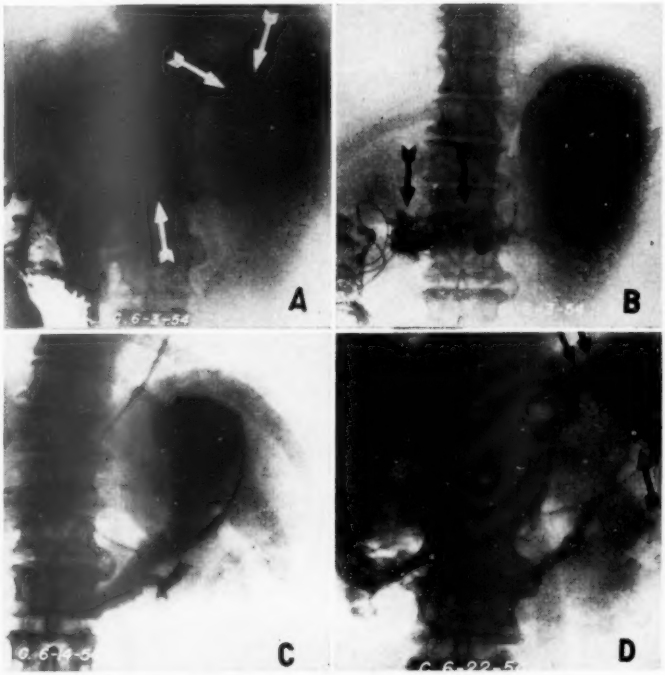


FIG. 9.—Resolution of a pseudocyst following sphincterotomy. This patient had a huge pseudocyst in the left upper quadrant. At operation, following aspiration of the cyst, a cholangiogram (A) through the cystic duct showed reflux up the pancreatic duct (arrow) and beginning filling of the pseudocyst (two arrows). Following sphincterotomy, a pancreatogram (B) was performed by injecting the duct of Wirsung. This filled the pseudocyst. Note visualization of the pancreatic tissue (2 arrows). Resolution of the pseudocyst was followed through a small plastic tube left in the pseudocyst. Note (C) that the cyst had shrunk about two-thirds in two weeks, and after three weeks (D) only a small residual space (arrow) was left. The solution passed down the pancreatic duct into the duodenum and refluxed back into the stomach (2 arrows).

is drained, a cutaneous pancreatic fistula may form by way of the retroperitoneal space, and may persist for months and years, due to spasm of the sphincter. Sphincterotomy, again, by reducing the intraductal pressure, will result in rapid closure of such a fistula. True acute cysts of the head will also disappear following sphincterotomy. Untreated, these cysts may become chronic and lose their connexion with the duct system. Cystojejunostomy is required in such cases.

The treatment of cysts and fistulas of the pancreas by sphincterotomy requires the presence of an unobstructed pancreatic duct. It is therefore mandatory that an operative pancreatogram be performed in all such cases. In the presence of partial obstruction by stone or

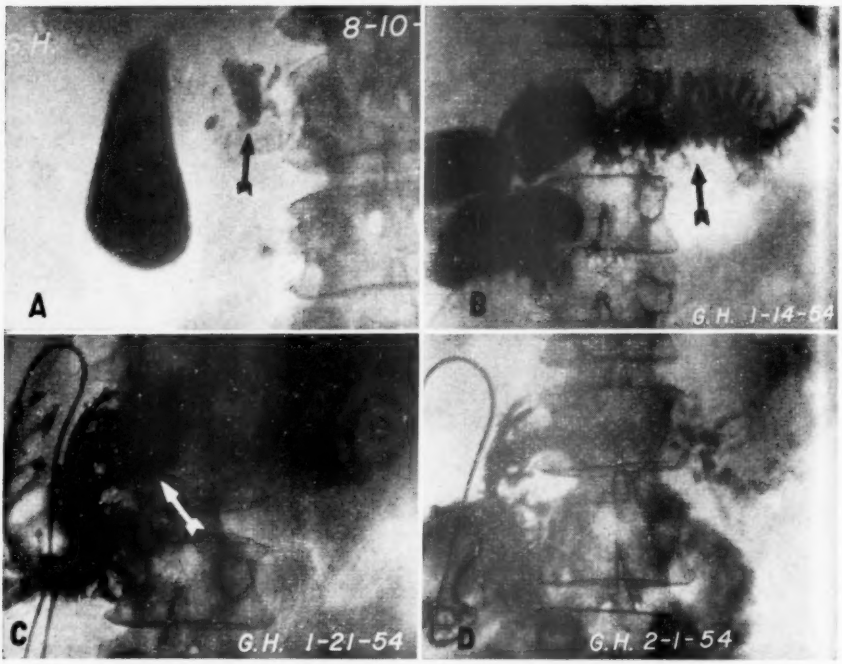


FIG. 10.—Partial obstruction of pancreatic duct by calculi. This patient had calcification (arrow) in the head of the pancreas (A). An operative pancreatogram (B) following sphincterotomy revealed enormous dilatation of the duct (arrow) distal to the partial obstruction. The head of the pancreas was incised, the stones removed, the incision closed, and the duct of Wirsung drained by the indwelling tube. Post-operative serial pancreatograms showed (C) beginning resolution of the cavity (arrow) which held the stones, and finally (D) reformation of the duct and marked reduction in its diameter.



FIG. 11.—Function of the duodenal wall following sphincterotomy. When sphincterotomy is properly performed the intact duodenal musculature prevents duodenal reflux by its pinch-cock action. A post-operative cholangiogram (A) shows the sphincter lying wide open (arrow). Following administration of morphine (B), the increased tonus of the circular muscle of the duodenal wall compresses the terminal part of the common duct (arrow) and acts as a one-way valve.

structure, either the obstruction is removed (Fig. 10 A–D) or if that is impossible a caudal pancreatico-jejunostomy is performed.

The disease process in pancreatitis is primarily that of recurrent attacks of acute inflammation, which may or may not produce areas of necrosis followed by replacement fibrosis. It follows that chronic pancreatitis is not a primary disease, but is one of the possible complications of recurrent acute attacks. If necrosis does not occur, the inflammatory œdema resolves and evidence of inflammation in the gland disappears.

The technique of sphincterotomy exploits the anatomical relationship of the sphincter of Oddi to the duodenal wall. Section of the sphincter for a distance of only 8–10 mm. does not interfere with the function of the duodenal wall as a one-way valve or pinch-cock. After a properly performed sphincterotomy, duodenal reflux does not occur (Fig. 11). The sphincter always heals in a position of retraction.

The regenerative power of the pancreas is as great as that of the liver. Our observations indicate that with reduction in intraductal pressure and cessation of recurrent acute attacks following sphincterotomy, the pancreas often regenerates. This has been demonstrated by serial secretin tests (Table I), and in several cases by histological evidence (Fig. 12).

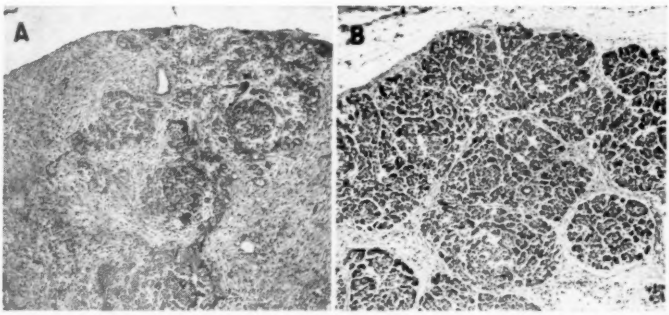


FIG. 12.—Regeneration of the pancreas following sphincterotomy. Biopsy taken at operation (A) showed infiltration, fibrosis and marked destruction of the acinar tissue. At autopsy four years later in the same patient, who died from another cause, histological section (B) shows almost complete regeneration of acinar tissue.

TABLE I.—REGENERATION OF PANCREAS AFTER SPHINCTEROTOMY (June 15, 1950) AS SHOWN BY THE SECRETIN TEST

Date	Total volume, c.c.	Total bicarbonate c.c., N/10	Total amylase, Lagerlof units
14/6/50	92	48	110
22/9/50	118	42	153
26/9/53	123	80	246
27/2/57	280	125	1,230

Once the pancreas has become injured as a result of reflux of bile into the pancreatic duct, it becomes susceptible to the noxious action of fat and alcohol. Intake of these substances will often produce a severe attack which cannot be prevented by sphincterotomy or any other operative procedure such as vagotomy, choledocho-jejunostomy, or pancreatico-jejunostomy. The mechanism of action of these substances is unknown, but it appears to be due to sensitivity of an injured pancreas to their metabolic products. However, once the pancreas regenerates, as evidenced by secretin tests, it no longer reacts to alcohol and fat imbibition. It therefore follows that sphincterotomy is but the first step in the treatment of recurrent pancreatitis. The patient must be kept on an alcohol-free and low-fat diet for a period of six to eighteen months, or until the pancreas regenerates, before cure of the disease can be considered successful.

Mr. Rodney Smith:

This disorder is, for some reason, a good deal less common in this country than in the United States, and I do not myself believe that the difference is accounted for solely by errors in diagnosis. It is a disease which can cause much disability due to incapacitating pain and not infrequently endangers life.

Rational therapy can only spring from a study of the ætiology and evidence strongly supports Dr. Doubilet's contention that reflux from the common bile duct through a common channel into the pancreatic duct is very often the cause of the recurrent acute attacks (*see* p. 630). If this reflux can be stopped, cure will result.

[Slides of biliary reflux were shown and a cine-film demonstrating the mechanism of the normal sphincteric apparatus at the lower end of the common bile duct and reflux occurring in chronic relapsing pancreatitis.]

In emphasizing the importance of biliary reflux, I am aware that there are certain apparent discrepancies which need explanation. The acute episodes occurring in relapsing pancreatitis are precisely similar to isolated instances of acute pancreatitis. Yet undoubtedly there are many causes of acute pancreatitis other than biliary reflux, and acute pancreatitis can occur in patients who have no true ampulla of Vater, the common channel necessary if reflux is to occur. Also a post-operative cholangiogram after choledochotomy for stone may show the contrast medium refluxing up the lower centimetre of the main pancreatic duct of a perfectly normal pancreas proving that reflux can occur without causing pancreatitis. An explanation is that while a normal pancreas may well be able to withstand minor reflux of bile, an attack of acute pancreatitis of any severity leaves a gland which is far from normal. One function of a normal pancreatic duct epithelium is to resist penetration by pancreatic ferments and after severe ductal damage during an attack of acute pancreatitis healing may take place with a lining incapable of resisting penetration. That some such change in permeability does in fact take place is shown by Dr. Doubilet's work on pancreatography, for contrast medium injected up the duct of an inflamed pancreas does not stay in the duct system but diffuses out and renders the whole gland opaque.

I suggest that it is the combination of two factors which causes relapsing pancreatitis; damage to the duct lining and biliary reflux, the latter ensuring that the ferments in the damaged pancreas are activated. The pancreas remains vulnerable and whenever further reflux of bile occurs a further attack of acute pancreatitis is likely to occur.

It is therefore logical to treat relapsing pancreatitis by trying to eliminate biliary reflux. The simplest method of achieving this is by the operation of sphincterotomy which, properly done, lays open the common channel so that the common bile duct and main pancreatic duct empty independently into the duodenum. In the majority of cases, therefore, where surgery is indicated for chronic relapsing pancreatitis, the first line of attack is sphincterotomy, which carries a low risk to life and offers an excellent chance of cure. It does not, however, cure every case of chronic pancreatitis and I should like to refer to several other procedures which have their place in surgical therapy.

Biliary diversion.—Reflux of bile up the pancreatic duct can be most effectively eliminated by dividing the common bile duct and reimplanting it into the duodenum or jejunum, but it is illogical to carry out this more severe procedure if the same result can be achieved by sphincterotomy. Sphincterotomy may be unsatisfactory and ineffective if œdema and induration of duodenum and pancreatic head have produced rigidity of the whole area, in this case biliary diversion may be the procedure of choice. Another infrequent indication for biliary diversion is compression and distortion of the lower common bile duct leading to partial obstruction and chronic biliary infection.

Retrograde pancreatic drainage.—This procedure is particularly indicated in those cases in which there is gross blockage of the pancreatic duct system with calculi and débris, the result of long-standing inflammation. Here, although biliary reflux may still cause intermittent exacerbations, the problem is pancreatic duct obstruction with undrained infection distally. Sphincterotomy, dilatation of the pancreatic duct, and trans-duodenal removal of pancreatic calculi may be quite inadequate if the whole duct system is packed with stones and débris. In this case, amputation of the whole of the body and tail of the pancreas may allow the duct system in the head of the gland to be cleared of all stones, and retrograde drainage established by anastomosis of the distal end of the duct to the stomach or to a jejunal Roux loop (Fig. 1).

Splanchnicectomy.—Splanchnicectomy can certainly have a useful effect upon the incidence and severity of pancreatic pain and therefore has a place in the treatment of chronic relapsing pancreatitis. It is claimed by some that splanchnicectomy also has a more direct effect and actually prevents pancreatitis by denervating and thus relaxing

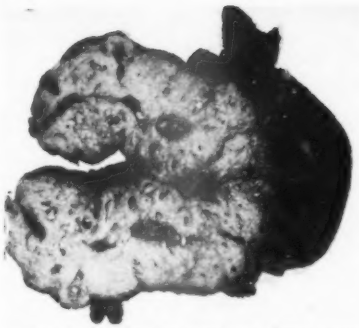


FIG. 1.—Operative specimen from a case of pancreatitis treated by resection of body and tail of pancreas and pancreato-gastrostomy.



FIG. 2.—Operative specimen from a case of pancreatitis treated by pancreato-duodenectomy. →

the sphincter of Oddi. Cine-cholangiographic studies have, however, failed to show any motor effects produced by splanchnic nerve block even though abolition of pancreatic sensation was complete. In my opinion splanchnicectomy cannot be expected to affect the frequency of exacerbations in relapsing pancreatitis, but it may be of symptomatic benefit in controlling chronic pain.

Pancreatectomy.—Distal pancreatectomy is occasionally indicated for chronic pancreatitis confined to the tail or body and tail of the gland. Such cases are rare, but may result from local trauma or changes in the blood vessels.

Pancreato-duodenectomy is an operation to be considered in those cases presenting with gross sclerosis, ductal obstruction, and calcification in the head of the gland (Fig. 2). The operation is carried out in the same way as for carcinoma of the head of the pancreas and the remaining body and tail of the gland treated by end-to-side pancreato-jejunostomy. The results of successfully performed operations of this kind are excellent, but it must be emphasized that technically the procedure is difficult or even hazardous, and Cattell and Warren (1953) have suggested that the wise surgeon will not embark upon it unless he has gained considerable familiarity with the technique by carrying out a number of resections for carcinoma. Certainly the immediate operative risk is sufficiently high to suggest that the operation should only be undertaken if it is felt that no other procedure has any chance of success.

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D . W. I. Card:

To the physician these patients present themselves either as a problem in undiagnosed abdominal pain, or with diarrhœa, steatorrhœa or in a state of poor nutrition. Pain is usually the more evident symptom in the earlier stages of a process which may last some years, while, as destruction of the gland advances evidence of overt pancreatic insufficiency becomes more prominent.

The pain is due to an increased pressure in the pancreatic duct system, at any rate in some instances. In one patient we were able to reproduce her pain exactly by stimulating the

pancreas with secretin and closing the sphincter with morphine. With this procedure flow into the duodenum ceased, to reappear when amyl nitrite was given, which simultaneously relieved the pain. These observations, which were carefully controlled, were repeated and are consistent with a concept of pain as due to increased intraductal pressure. Following sphincterotomy morphine failed to stop the flow of juice produced by secretin and no pain occurred. After this operation the patient remained free from pain for two years. If pain can be reproduced in this way then sphincterotomy should relieve it. With the use, if necessary, of morphine antagonists and amyl nitrite, the procedure is safe but of limited diagnostic value.

In the differential diagnosis of pancreatic pain we have had difficulty in distinguishing carcinoma of the pancreas from a benign duodenal ulcer infiltrating the pancreas and producing the syndrome which Rivers (1947) first described. We have also observed attacks of pancreatic pain in association with a perivaterian diverticulum.

The treatment of the attack of pancreatic pain should aim at preventing pancreatic secretion by continuous aspiration of stomach contents to stop hormonal action and by full doses of atropine to block vagal action. The pain can be controlled by morphine and pethidine while nitroglycerin half-hourly helps to relax the sphincter.

Pancreatic insufficiency.—Before this state is clinically obvious, various laboratory tests may show abnormalities, in particular tests of external pancreatic secretion. Using secretin and pancreozymin stimulation of the pancreas with an 80-minute collection, the volume, bicarbonate concentration and output, and the concentration and outputs of amylase, tryspin, and lipase have been measured (Marks and Tompsett, 1957). The values for all the enzymes run roughly parallel and it seems only necessary to measure the amylase level. It can be shown that the amylase figures can be quite abnormal even though the volume and bicarbonate values are normal. A measure of the amylase output with this form of stimulation seems the most sensitive single test of external pancreatic secretion. Tests of external pancreatic secretion have been criticized by some workers in the past as providing little useful diagnostic information but these criticisms are unjustified unless pancreozymin, a specific enzyme stimulant, is used. In order to avoid the tedium of intubation, provocative serum amylase tests have been proposed whereby the level of the enzyme is measured in the blood stream after stimulation by secretin and pancreozymin. In our hands this method has not been very useful. In the latter stages of chronic pancreatitis we have found the glucose tolerance test of great value in distinguishing the steatorrhœa of pancreatic disease from that of malabsorption. In pancreatic disease we tend to find a diabetic or pre-diabetic curve whereas in the malabsorption syndrome we find a flat curve. The extent of the steatorrhœa and creatorrhœa does not allow us to distinguish between diarrhœas of pancreatic origin and those occurring with the malabsorption syndrome.

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Section of Medicine

President—G. E. BEAUMONT, M.A., D.M., F.R.C.P., D.P.H.

[*March* 26, 1957]

DISCUSSION ON DIAGNOSTIC FEATURES OF SOME PANCREATIC DISEASES

Dr. T. C. Hunt: So-called chronic pancreatitis includes at least two types of case, one of which is correctly described as chronic relapsing pancreatitis, and this may be sufficiently clear-cut and characteristic to enable a clinical diagnosis to be made with considerable confidence. Another is a painless type also with fairly typical features—but there are variable clinical cases between these two which are of uncertain ætiology and inconstant symptomatology.

The diagnosis of chronic relapsing pancreatitis on clinical grounds may, however, be difficult and not easy to confirm either by the laboratory or at operation. There is no laboratory test available which is able consistently to establish the diagnosis—a deficiency which should be remedied.

I have reviewed my own cases during the past eight years and also, with the kind permission of several of my colleagues at St. Mary's Hospital to whom I am very grateful, the notes of 21 other cases mostly proved at operation or post-mortem. The uncertainty of clinical diagnosis is shown by the number of doubtful cases in this series—only 59 being acceptable out of 108 suspected or presumptive diagnoses.

Chronic relapsing pancreatitis is not only difficult to diagnose *from* other conditions but is often associated *with* other conditions in many cases. In 59 cases I have found that the conditions most frequently associated with chronic relapsing pancreatitis were gall-bladder disease in 14, duodenal ulcer in 7, and neurosis in 21. This incidence of gall-bladder disease is rather lower than in some series as is that of duodenal ulcer; the considerable degree of neurosis often present is usually a result of the pancreatitis and does not precede it. In part, the superadded nervous symptoms seem to arise from the patient's determination to convince the doctor that he has severe pain and the frustration he feels when normal X-rays are regarded as proof that his symptoms are psychological. It is interesting in connexion with the occurrence of duodenal ulcer that hæmatemesis and melæna may occur in chronic relapsing pancreatitis with no evidence of chronic ulcer at any time. Such hæmorrhage occurs during an acute attack with the typical pain of pancreatitis, and though possibly due to an acute erosion, is not easy to explain.

Of these 59 cases 28 were male and 31 female. The average age of onset was 46 and symptoms had persisted for an average duration of nine years when first seen by me. In 3 cases the age of onset was under 15 and in 12 it was over 60.

The principal clinical symptom in chronic relapsing pancreatitis is pain, the other main clinical features being given in Table I.

TABLE I.—CHRONIC RELAPSING PANCREATITIS, 59 CASES

Main Clinical Features

	Cases		Cases
Pain	56	Glycosuria	5
Loss of weight	41	Calcification	4
Vomiting	32	Pancreatic calculi	3
Jaundice	10	Cysts (palpable)	2
Steatorrhœa	6		

Loss of weight is often extreme and in 22 cases was over 2 st. Vomiting is often severe but does not bring relief of pain.

Of these 59 cases the diagnostic triad of steatorrhœa, calcification and glycosuria occurred in only 5, and of these cases 3 developed without any pain at all. Palpable cysts occurred in 2 cases, in both of which pain was severe and continuous.

The pain of this disease may arise suddenly. It may be so violent that the patient collapses at work, but more often it develops over a few hours and increases gradually to a crescendo. It is usually continuous, but in a few cases comes in waves so that the distinction from intestinal colic may be difficult. Patients often describe it as excruciating or agonizing and may roll about and sweat. One doctor patient said it felt as if a piece of bowel was being stretched.

Out of 51 patients the pain was central in the epigastrium in 22, in 2 of whom it was also substernal. In 13 it was limited to the right side of the upper abdomen, in 8 to the left side, whilst in 8 it was both central and one-sided.

In about one-third of the patients—19 out of 51—the pain radiated into the back, a somewhat surprisingly low proportion, but in none did it radiate into the neck or arms which is a helpful point in excluding coronary infarction.

The pain, I have noticed, is sometimes strikingly better sitting up than lying down, in contrast to the pain of ulcer which is usually the reverse. When vomiting occurs it does not relieve the pain, and in a very few cases diarrhœa follows the pain.

In general attacks of the disease last from a few hours up to many days, the average in this series being three-and-a-half days. As a rule they are more severe and of shorter duration than the periodic attacks of duodenal ulcer. There is only rarely any direct precipitating cause but fatigue and chill sometimes seem to provoke attacks and undoubtedly in a few cases extra indulgence in alcohol. Most patients are completely free between attacks with no pain or other symptoms, but are often cautious in their eating habits especially as regards alcohol and hot fatty foods.

The diagnosis of chronic relapsing pancreatitis from duodenal ulcer may be very difficult. In the latter the sex incidence is predominantly male and attacks more often begin between the ages of 20 and 40 than between 40 and 60. Vomiting and pain and loss of weight are usually more marked in the former. Attacks of chronic pancreatitis are associated with a slight or moderate pyrexia and leucocytosis in a proportion of cases: and bed rest, alkalis and food, which produce little or no relief in chronic pancreatitis, often do so in ulcer.

Mr. Rodney Smith: I shall discuss the diagnostic problems in two major types of lesion, namely carcinoma and relapsing pancreatitis.

Carcinoma.—Professor Charles Rob and I recently analysed symptoms and signs in 190 patients with carcinoma of the pancreas or ampulla of Vater (Tables I and II).

TABLE I.—FREQUENCY OF MAIN SYMPTOMS

Symptoms	No. of patients	Comment
Pain	131	Present in 50% of ampullary carcinomas, 90% of carcinoma of the head, 100% of carcinoma of the body
Jaundice	128	Present in all ampullary carcinomas and in 94% of carcinoma of the head
Loss of weight	163	
Lassitude and anorexia	84	
Diarrhœa	61	
Itching	58	
Vomiting	43	
Tumour noticed by patient	16	
Enlarged lymph nodes	9	

TABLE II.—THE FIRST SYMPTOM

	Pain	Jaundice	Others
Head of pancreas or ampulla of Vater	59	54	14
Body or tail	49	0	8

It is particularly noteworthy that pain proved to be such a common symptom, not only in carcinoma of the body and tail but also in cases of malignant obstruction of the lower end of the common bile duct, when it was the first symptom complained of as often as was jaundice.

The "painless jaundice" still emphasized in many textbooks is thus a misleading term, at any rate if it is held to imply that painful jaundice cannot be caused by a carcinoma.

It was further observed in the series studied that fluctuation in the degree of jaundice was not uncommon, particularly in cases of ampullary carcinoma, probably caused by central sloughing of a friable tumour intermittently relieving total biliary obstruction. The observation previously recorded by others was confirmed that while a palpable dilated gall-bladder in a case of obstructive jaundice (Courvoisier gall-bladder) nearly always means malignancy, failure to feel a dilated gall-bladder means nothing and certainly cannot exclude a carcinoma. The gall-bladder may be fibrosed by previous disease; the growth obstructing the common bile duct may have extended to obstruct the junction of the cystic duct and common duct, thus preventing distension of the gall-bladder; the gall-bladder may be dilated but tucked under the liver and not palpable through a fat abdominal wall.

Of the special investigations usually carried out, mention must be made of radiography. In the hands of a radiologist with particular interest and experience a barium meal will show abnormality in some 50% of cases of carcinoma in this region. Oral or intravenous cholangiography seldom provides evidence of any value and is contra-indicated in jaundice of any depth. Percutaneous trans-hepatic cholangiography (Nurick, Whiteside and Hickey,

1953, *Brit. J. Surg.*, **41**, 27; Smith, Rodney, 1954, Progress in Clinical Surgery, London) can very often demonstrate the site and size of a carcinoma very clearly, but the risks of leakage of bile into the peritoneal cavity, calling for immediate laparotomy, are sufficiently high to suggest that this method of investigation should only rarely be employed.

The final investigation is laparotomy. Even here the diagnosis may be in doubt, for a common source of uncertainty is the enlarged irregular head of pancreas in a jaundiced patient, which could be either malignant or inflammatory. Here the state of the common bile duct will usually provide the answer. If it is grossly dilated, thin-walled, translucent and free from signs of inflammation, this means malignancy. Conversely the jaundice caused by pancreatitis is usually due partly to obstruction and partly to biliary infection and the common bile duct is moderately dilated or even not dilated at all, thick-walled, opaque, inflamed and with adherent peritoneum. In cases of real doubt, biopsy may be performed but not from the surface of the pancreas. This may well miss a deeply-placed carcinoma and carries a high risk of causing a pancreatic fistula. Biopsy from within the duodenum after anterior duodenotomy is permissible, but even this should be avoided when possible.

Chronic relapsing pancreatitis.—Dr. Hunt has dealt with many of the problems of clinical diagnosis. I would agree with him that in a fair proportion of cases a characteristic clinical picture leads to a diagnosis of pancreatitis but confirmatory evidence from laboratory investigations is lacking. It is true that during acute exacerbations, elevation of serum amylase and possibly lipase may be found but this is not invariable. Plain radiography and intravenous cholangiography may reveal pancreatic calcification or a distorted common bile duct but again X-rays are often normal. Tests of pancreatic function seldom show any abnormality until gross destruction of the gland has taken place.

In many cases of relapsing pancreatitis a clinical diagnosis has to be made, unsupported by other evidence, and it becomes necessary to carry out the final investigation—exploratory laparotomy. With the abdomen opened it is not usually difficult to decide whether the pancreas is the site of inflammation of any severity. Once the diagnosis is confirmed, it is the duty of the surgeon in carrying out a general examination of the abdominal viscera to pay particular attention to the biliary tract, and to try to assess not only the degree of pancreatitis but also the probable ætiological factors.

In a very high percentage of cases reflux of bile into the pancreatic duct from the common bile duct is important. This has been shown very clearly by cine-cholangiographic studies carried out on patients with relapsing pancreatitis.

A film "Cine-cholangiography in Chronic Relapsing Pancreatitis" was shown.

The state of the bile passages at operation should be studied, cholangiography being used in some cases, and, if sphincterotomy is carried out, catheterization of the main pancreatic duct is performed and an operative pancreatogram obtained.

To sum up then, clinical assessment should normally be followed by a cholecystogram and intravenous cholangiogram, a barium meal, estimation of serum amylase and lipase, particularly during an acute episode, and possibly tests of pancreatic function, though the value of these is very limited. If all these investigations are negative, it is logical in many cases with incapacitating symptoms to proceed to exploratory laparotomy.

Dr. Martin Bodian: My contribution on diagnostic features of some pancreatic diseases in childhood is largely based on personal pathological observations made over the period 1943 to 1956. The data have been selected from a material of about 2,500 autopsies but occasional biopsy findings have also been included.

The distribution of the material and the frequency with which individual conditions were encountered is given in Table I.

TABLE I.—PANCREATIC DISEASES 1943 TO 1956

	No. of cases
Fibrocystic disease of the pancreas	123
Congenital hypoplasia of the exocrine pancreas	3
Congenital cystosis of the pancreas	1
Pancreatitis due to various causes	7
due to congenital syphilis	10
due to cytomegalic inclusion disease	2
Diabetes mellitus	2
Hypoglycæmia	2
Annular pancreas	several
Ectopic pancreas	several

The most commonly encountered condition manifesting pancreatic pathology in our hospital experience is that of *fibrocystic disease of the pancreas* or congenital mucosis which accounted for about 5% of our autopsies.

Our basic conception of this disorder is that it is a recessively inherited congenital anomaly of mucus-secretion manifesting itself with an unduly viscous mucus which, because of its tenacity, tends to be retained in the various channels through which it normally flows freely. This abnormality would only be observed in those organs where mucus is produced and these belong almost exclusively to two major systems in the human organism, namely the respiratory system and the alimentary system which includes the gastro-intestinal tract and its adnexæ, the salivary glands, the pancreas and the liver. It will be noted from this concept that this disorder is widespread and that the involvement of the pancreas is by no means exclusive nor, for that matter, all-important. It is also our belief that the basic anomaly in this condition, the "mucosis", leads to a series of complications in different organs and that the clinical manifestations of the disease and its progression are entirely related to these complications and not to the basic lesion by itself. Thus there will be retention of secretion of mucus first of all in some of the smallest ductules of the pancreatic duct system leading to blockage of enzyme-containing secretion in the acini which are drained by these ductules. The retained secretion will lead to increasing flattening and then atrophy of the acinar epithelial cells but when the metabolism of these cells is sufficiently disturbed by the mechanical pressure exerted on them, the enzymes contained in the acinar lumen (notably the locally activated trypsin) will attack these epithelial cells and destroy them, producing a focal pancreatic necrosis. This will be followed by reactionary infiltration with inflammatory cells, later by fibroblasts and ultimately fibrous tissue will replace the area of pancreatic necrosis. More and more areas of pancreas will thus be destroyed, more and more ducts will be blocked by the abnormal secretion and there will be a progressive diminution of the enzyme-producing capacity of the pancreas: such pancreatic juice as is being produced would not be capable of passing through the blocked duct system into the duodenum.

It should be noted that the main pancreatic duct is not atretic (and we have shown this by means of serial sections) but that such blockage as may be seen ultimately is purely a late sequel to the abnormality of secretion. Ultimately the pancreas is reduced to a mere fibrous core with few residual ducts and acini showing the changes of mucosis and with reasonable numbers of islets. This core is surrounded by a cushion of lipomatous tissue.

The original idea that meconium ileus, a form of neonatal intestinal obstruction in fibrocystic disease of the pancreas, is due to atresia of the pancreatic duct and failure of the meconium to be digested owing to lack of trypsin in the gut, is completely fallacious. The abnormality of meconium is merely a reflection of the mucus anomaly in the glands of the gastro-intestinal tract and it should be remembered that meconium is almost exclusively mucous in nature.

Meconium ileus was seen in some 30% of all the fatal cases of fibrocystic disease of the pancreas or in 15% of all the cases, including survivors. Once meconium has been passed, fæcal intestinal obstruction is only rarely seen.

The clinical manifestations of the pancreatic pathology in fibrocystic disease are those of digestive disability with normal absorption of predigested foods such as glucose or amino acids. They lead in the untreated case to failure to thrive in spite of a voracious appetite and enormous wastage of undigested foods in the stools which are large, bulky and offensive.

Other pathological manifestations of this widespread disease are seen in the salivary glands, notably in the sublingual glands. There the lesion is that of pure mucus-retention without complications, hence asymptomatic.

The liver lesions are those of retention cysts in the finest bile ductules beneath the capsule with proliferation of other bile ducts in an effort to overcome the obstruction. This biliary pathology is accompanied by some atrophy of adjacent liver cells and by some increase in fibrous tissue in the affected portal areas. The lesion is focal and has been designated focal biliary fibrosis. In most instances it is asymptomatic, since there is usually ample liver tissue available which is normally functioning. Occasionally, however, and more commonly as these children grow older, more widespread cirrhotic liver lesions manifest themselves even with symptoms of liver failure and of portal hypertension.

Finally, and most important, there are the widespread lesions in the respiratory system. These again are the sequelæ to mucus-retention leading to obstructive and to inflammatory lesions in the bronchial tree and lung parenchyma with emphysema, atelectasis, bronchiolitis, bronchiolectasis, bronchopneumonia, bronchiolar abscesses, bronchitis and bronchiectasis. These complicating lesions of the respiratory tract are, to some extent, amenable to treatment with modern antibiotics. Life can now be prolonged in many cases but the struggle between antibiotics and bacteria in an effort to prevent permanent serious structural changes in the lungs with its cardiac sequelæ is by no means easy.

I have not yet mentioned the finding in recent years of an increased sodium chloride content in the sweat in these children. It is difficult to explain this observation on the basis of the concept of mucosis unless one assumes that the abnormal enzyme mechanism which is

probably responsible for the mucus abnormality is also concerned in the regulation of the salt content of the sweat.

Regarding the other conditions mentioned in Table I, I shall merely touch upon some principal data:

Congenital hypoplasia of exocrine pancreas.—Of this rare condition we have seen three examples. I have personally seen a further 4 cases from outside sources but have not included these in my survey.

This is a failure of the duct and acinar system to form fully and in some instances there are mere vestiges of acini with a poorly-formed duct system, in others there are no acini at all. The islets are well developed and they, as well as the vestiges of ducts and acini, lie in a stroma of lipomatous tissue. There is no fibrosis, no cellular infiltration and no retention cysts in the pancreas, nor is there any evidence of mucosis in any other tissue.

These children present symptoms of pancreatic deficiency and show no trypsin in their duodenal juice. They simulate in this respect fibrocystic disease but they are also liable to respiratory infections. Moreover the incidence of this disease in two siblings has been reported. The liver is usually the seat of severe fatty infiltration which may be followed by diffuse hepatic fibrosis.

Congenital cystosis of the pancreas: Of this we have seen one example not associated with cystic disease in any other organ. Conversely, none of the 4 cases of polycystic disease of the kidneys (1 with cystic disease of the liver) has shown cysts in the pancreas.

The clinical picture was that of pancreatic deficiency with absent trypsin from the duodenal juice. The child died from inanition at the age of 6 months having overcome an attack of respiratory infection. At post-mortem there were numbers of true cysts but the pancreatic ducts were patent and there was no fibrosis except in the immediate vicinity of the cysts. The pancreatic achylia was attributed to an associated absence of zymogen granules from the pancreatic acini which were otherwise normal.

Interstitial pancreatitis of various causes.—This small group of 7 cases does not manifest a uniform pathology. It includes one child, aged 3 years, with chronic interstitial pancreatitis (pancreatic fibrosis) probably secondary to polyarteritis nodosa; another child, aged 3 years, with a terminal pancreatic necrosis with widespread fat necrosis of the peritoneum associated with an acute duodenitis; one newborn mongol infant with a hepato-pancreatitis, probably a complication of neonatal virus hepatitis and a manifestation of a transplacental infection; one newborn infant with chronic interstitial pancreatitis, associated with meconium peritonitis; finally a more uniform small group of 3 infants, aged, 6/12, 6/12 and 9/12.

These 3 cases showed the clinical picture of gastro-enteritis with predominant vomiting in one and were found to be cases of isolated interstitial pancreatitis, associated with a severe enteritis in two. The duct pathology suggests an ascending infection from the duodenum. None of these cases showed at autopsy any evidence of generalized mucous gland disease (mucosis) and the pancreatic pathology was unlike that in fibrocystic disease.

There were also 10 cases of interstitial pancreatis due to *congenital syphilis*, all showing an associated severe pericellular hepatitis.

Two cases of *disseminated cytomegalic inclusion disease* showed some pancreatic involvement both of exocrine and duct tissue with areas of focal inflammatory cell infiltration and interstitial fibrosis.

Finally, I shall refer briefly to a few other conditions seen:

2 fatal cases of *diabetes mellitus* showed a striking paucity in islet tissue and there was hyaline degeneration of islets in 1.

2 cases of hypoglycæmia with fits were explored in order to identify an islet adenoma, if present. No disease was found in the pancreas of 1, but the other showed a diffuse islet hyperplasia with particular predominance of beta cells which constituted about 90% of the islet cells.

There were several instances of annular pancreas which is a ring-like extension of the head of pancreas around the descending duodenum and which is commonly associated with other malformations such as malrotation, duodenal stenosis or atresia, and mongolism.

The more severe forms produce obstructive symptoms in infancy but less severe variants may lead to symptoms of duodenal obstruction only in later childhood or adult life. The case of pancreatic necrosis associated with duodenitis had an annular pancreas and was an example of this later symptomatic manifestation. Treatment is by duodeno-jejunostomy.

There were also several instances of ectopic pancreatic islets associated with Meckel's diverticula. One particular instance was of theoretical interest in that it occurred in a case of meconium ileus with fibrocystic disease of the pancreas. The ectopic tissue showed a replica of the changes in the main pancreas illustrating that this pathology is not conditioned by obstructive disease in the main pancreatic ducts but is a manifestation of the abnormality of secretion, a dyschylia.

[*May* 28, 1957]

DISCUSSION ON SOME BLOOD DISORDERS

Hypersplenism

By M. C. G. Israëls, M.D., F.R.C.P.

(*University Department of Hæmatology, Manchester*)

The idea of a primary disease due to over-activity of the spleen was suggested about ten years ago by Doan, Dameshek and their colleagues in the U.S.A.

The essential criteria for diagnosis were: (1) An enlarged spleen. (2) Depression of one or more of the red cells, granulocytes, or platelets in the peripheral blood—anæmia, granulocytopenia or thrombocytopenia. (3) Activity in the bone-marrow of the cell series depressed in the peripheral blood; e.g. anæmia accompanied by intense erythroblastic activity in the marrow.

It followed that if these three criteria were met, the proper treatment for the patient was removal of the spleen. Then, presumably, relieved of the excessive sequestration and destruction in the spleen of the affected cells, the blood count would return to normal and the patient would be cured of his symptoms. This response made a fourth criterion.

Our attitude to primary hypersplenism has slowly changed as causes have been found for many of the cases originally labelled primary, and now a case can be made out for doubting the existence of the syndrome.

In 1950 a note of caution appeared in the work of Dameshek and Estren and a fifth point was added to the criteria, viz. that the histology of the spleen must be normal. This meant that the clinical diagnosis of primary hypersplenism was always open to histological correction.

No one will deny that a syndrome of secondary hypersplenism exists. If cells are unusually sequestrated in the spleen, they will be destroyed more rapidly. The classical example is congenital spherocytosis in which the anæmia is largely relieved by removal of what is often a grossly enlarged spleen. But the *primary* defect is the congenitally abnormal shape of the red cells, and the histology of the spleen is far from normal, showing over-filling of the pulp with red cells and resultant compression of the other splenic structures.

The classical example of primary hypersplenism was considered to be the syndrome known as acquired hæmolytic anæmia. Here there is grave anæmia, the bone-marrow shows intense normoblastic activity with pro-erythroblasts present; the spleen is much enlarged and on section the main structure remains normal, the only abnormality being some hyperplasia of reticulum cells in the sinuses.

But we have learnt from experience that splenectomy often only partially relieves the anæmia in this disease. The advent of the Coombs antiglobulin reaction has enabled us to establish the presence of hæmolytic antibodies which had been long suspected. Nowadays most of these patients are successfully controlled by cortisone treatment and splenectomy is only carried out on the few who fail to respond. It is clear that acquired hæmolytic anæmia is not a primary hypersplenism; the spleen is probably taking part in the production of abnormal antibody and its normal activity of sequestration and destruction of red cells is increased because the red cells affected by the antibody have a much shortened survival. The hypersplenism is only part of the pathological picture in this disease.

In another group, the presence of a large spleen as the sole clinical finding together with typical findings in the blood and bone-marrow have led to splenectomy; but the sections of the spleen have shown that one or other of the reticuloses is present and the prognosis is that of the primary condition (Israëls, 1953).

Splenic neutropenia is a rare syndrome. I have seen patients with chronic neutropenia but without enlarged spleens; the two patients with enlarged spleens and neutropenia but no anæmia or thrombocytopenia have turned out to have chronic infections and we have not yet removed their spleens.

From experiences such as this, it is clear that splenomegaly and primary hypersplenism may well be a non-existent combination. We do know that hypersplenism can arise during the course of another blood disease and that the effects can be temporarily alleviated by splenectomy. The cases of hypersplenism occurring in the course of chronic lymphatic leukæmia and in myelosclerosis are examples.

For all these reasons the combination of a large spleen with anæmia, granulocytopenia or thrombocytopenia means a *secondary* hypersplenism, and whether we recommend splenectomy will depend on what we think the primary disease is likely to be.

Thrombocytopenic purpura does appear to be a form of hypersplenism which fulfils the criterion that splenectomy will be effective. In a series of 65 cases of thrombocytopenic purpura who had the spleen removed, 73% showed a completely satisfactory response; i.e. the purpuric manifestations disappeared and the platelets rose to normal levels and stayed there; in 19% the platelets stabilized at a subnormal level and the patients continued to have minor purpuric symptoms; in only 5% did the operation fail completely. In thrombocytopenic purpura, there is thrombocytopenia, an active marrow containing megakaryocytes, a good response to splenectomy, and the histology of the spleen shows no abnormality of the main structure; sometimes there is reticulum-cell hyperplasia in the Malpighian bodies. But there is never a palpably enlarged spleen, indeed it is axiomatic that if the spleen is very large, the condition is not primary. At operation the spleen is usually found to be two or three times as large as normal, but this does not make it palpable in the normal person. So in the sole survivor of the primary hypersplenic syndrome, we are paradoxically denied the sign of a palpable enlarged spleen. The work on anti-platelet antibodies may place thrombocytopenic purpura in the same class of diseases as acquired hæmolytic anæmia. So far the evidence is too conflicting for acceptance (*Lancet*, 1955) and so far thrombocytopenic purpura remains an apparently primary hypersplenism.

The physician should recommend splenectomy in this group of diseases in three conditions:

(1) In thrombocytopenic purpura, after a sufficient time, usually one month, has been allowed for spontaneous remission or for cortisone to induce a remission.

(2) In congenital spherocytosis, because experience has taught us that relief can be expected in 99% of cases.

(3) In follicular lympho-reticulosis, where diagnosis is possible. The points are a grossly enlarged spleen, a patient who is remarkably well in spite of his abdominal mass and blood abnormalities, and the spleen puncture should show only lymphocytes.

In all other cases splenectomy should be avoided if possible. Sometimes splenectomy is recommended as a diagnostic measure and in the hope of temporary relief. But the prognosis should then be very guarded.

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Recent Advances in the Diagnosis and Treatment of Hæmophilia

By ROSEMARY BIGGS, M.D.

(*Department of Pathology, Radcliffe Infirmary, Oxford*)

DURING the last three to four years we have seen nearly 200 patients with constitutional hæmorrhagic diatheses. The vast majority had hæmophilia and it is for that reason that most of our efforts have been concentrated on the study of this condition. Christmas-disease patients constitute about 10% of the total and patients with the fairly recently described plasma thromboplastin antecedent (P.T.A.) deficiency are very infrequent. The distribution differs in different parts of the world. In Switzerland Christmas disease is more common. In New York it appears that P.T.A. deficiency is almost as frequently encountered as hæmophilia. These distribution differences are difficult to understand.

Hæmophilia is inherited as a sex-linked recessive character, but nearly half of the patients give no history of any other affected person in the family. In these instances, either the inheritance is obscured by successive transference of the gene through generations of normal females, or the condition has arisen anew by mutation.

Hæmophilic patients have a defect in blood coagulation probably due to the deficiency in or absence of antihæmophilic globulin (A.H.G.), a substance necessary for normal coagulation. It is possible to measure this substance in the blood and the severity of bleeding is at least approximately related to its level. The classical case of hæmophilia is easily recognized. The patients suffer from repeated episodes of bleeding which include massive hæmatomata, hæmarthroses and bleeding from the nose, gastro-intestinal tract and kidneys. Many of these episodes are not clearly associated with trauma. Usually by adolescence the patient's joints are crippled as the result of multiple hæmarthroses. Laboratory tests show a long clotting time and complete absence of antihæmophilic globulin; 60–80 of our patients come into this category. The amount of disability depends partly on chance, temperament and the amount of care his mother takes.

In addition to these severely affected patients are a number who are much more mildly affected. In our series of such patients from 48 different families the proportion of mildly

affected cases is probably high because it is in these patients that difficulty in diagnosis arises. They live normal lives and hæmorrhage is nearly always related to definite trauma. Hæmarthroses are uncommon and the joints never show any permanent damage.

Analysing the results for all the mildly affected patients the A.H.G. levels have varied between about 1 and 30%. Practically all of the patients with more than 5% of A.H.G. are very mildly affected but we have seen patients whom we consider have hæmophilia with as much as 30% and 2 patients of rather doubtful diagnosis with more than 30%.

It is of interest to see what happens when these patients are subjected to operation. Since the bleeding tendency is usually disclosed only by trauma quite a high proportion of patients give a history of previous dental extraction or operation. 26 gave a history of dental extraction and without treatment all had bled for a week or more and 7 required transfusion.

12 patients gave a history of previous tonsillectomy and 2 patients told us that an affected relative had died after tonsillectomy. The A.H.G. levels and history of transfusions in these patients is shown in Table I. Patients with more than 15% A.H.G. do better than

TABLE I.—TONSILLECTOMY IN MILDLY AFFECTED HÆMOPHILIC PATIENTS

Case	Level of A.H.G.	Course of convalescence	Transfusion
1 (relative)*	6	Died	?
2	6	Bled excessively and became very anæmic	None
3	9	Excessive bleeding	Daily for 7 days
4	9	" "	Transfused
5 (relative)*	10	Died	?
6	10	Excessive bleeding	10 pints
7	15	" "	None
8	20	" "	None
9	22	" "	Transfused
10	25	" "	None
11	25	" "	Transfused
12	30	" "	None
13	39	" "	None
14	48	" "	None

*Information supplied by affected relatives seen by us.

those with less than 10%. 7 patients had had appendicectomy and this operation was surprisingly uneventful. Table II shows the remaining operations. Again patients with the most A.H.G. have done best.

TABLE II.—MISCELLANEOUS OPERATIONS ON MILDLY AFFECTED HÆMOPHILIC PATIENTS

Case	Operation	A.H.G. level	Course of illness	Transfusion
20	Laminectomy	0–4	Very excessive bleeding	Daily for 6 weeks
21	Excision of piece of lip	4	3 months in hospital	Transfused
22	Glands of neck	4	2 months in hospital	None
17	Hæmangioma	10	Excessive bleeding	Numerous
17	Hæmorrhoidectomy	10	" "	"
23	Circumcision	10	" "	?
24	Circumcision	11	" "	?
25	Circumcision	12	" "	None
26	Abscess of buttock	15	" "	Transfused
27	Gastrectomy	15	" "	2 transfusions

Two general inferences emerge from the study of these patients. One is that bleeding is likely to occur in hæmophilic patients with A.H.G. levels up to 30%. In treating severely affected hæmophilic patients whose initial level of antihæmophilic globulin is 0, no significant reduction in their bleeding tendency is likely to be achieved unless the level of antihæmophilic globulin can be raised above 15%. Surgical procedures will not be safe unless the level can be raised above 30%.

TREATMENT OF HÆMOPHILIA

A.H.G. is present in plasma and can also be separated from plasma in a more or less concentrated form. We have observed the effects of surgical treatment in hæmophilic patients both after fresh human plasma and after concentrated animal A.H.G. I shall discuss the treatment of severely affected patients.

Human Plasma

One of the difficulties in using human plasma is that the A.H.G. is very unstable and the plasma must either be used quite fresh (within hours of collection) or it must be stored with special precautions to prevent deterioration. We have found that storage at −30° C. may give adequate levels even after one to two months.

1,000 ml. of human plasma given to an adult hæmophiliac in 45–60 min. usually raises the level of A.H.G. to about 25%. Very occasionally, patients have a greater rise, some seem resistant to treatment and the rise is much less. The level achieved by plasma transfusion, in fact, seldom raises the hæmophiliac out of the hæmophilic range. This treatment does, however, bring the severely affected patient into the very mildly affected range.

For minor procedures such as dental extractions, this treatment reduces the bleeding under favourable circumstances but does not eliminate it altogether. We have found that with plasma treatment it is sometimes reasonably safe to remove as many as 12–16 teeth at one time. This policy is, however, undoubtedly hazardous and should not be undertaken without more potent antihæmophilic material available in case of emergency.

Treatment with Animal A.H.G.

The effects of a litre of plasma suggest that the dose of A.H.G. to reach a safe hæmostatic level must exceed 2 litres. Thus concentrated A.H.G. must be able to supply doses equivalent to 2–3 litres of human plasma in a reasonable volume of diluent. A mistake that has been made in the past is to assume that quite small amounts of A.H.G. are effective when to get a reasonable dose it would be necessary to dissolve the contents of 50–100 ampoules. This era is now passing and it is realized that to enter the ampoule scale in A.H.G. the material requires to be purified 2,000 to 10,000 times.

We have used concentrated animal A.H.G. initially for volunteers who needed dental extractions. 5 of such volunteers were treated and in all good solid clots formed in the sockets; in 3 healing was uneventful. One patient developed thrombocytopenia and on further investigation it was found that beef blood contains a species agglutinin for human platelets. This agglutinin is in the fraction containing A.H.G. Also one patient had an early allergic reaction. As a rule the low platelet levels are very temporary and do not affect hæmostasis. But the one exceptional case who was adversely affected ordinarily had a rather low platelet count and was taking Epanutin for epilepsy. A.H.G. made from pig blood does not have this platelet-agglutinating effect.

Both pig and beef A.H.G. are antigenic and, so far, we have never attempted to give more than one course of treatment, that is ten days of daily injections of material from one animal species. For this reason after the first volunteers the animal A.H.G. has been used only for patients who are liable to die unless they are treated with animal A.H.G.

Patients treated surgically who received animal A.H.G. included (1) a young man who had received an accidental gunshot wound of the back and arm and required the removal of a traumatic arteriovenous aneurism from the brachial artery. His case is described in detail by Fraenkel and Honey (1955). (2) A young man who had a head injury from a motor cycle accident, and (3) a boy of 15 who had an operation involving the removal of laminæ from 12 vertebræ for the treatment of a massive extradural clot.

The present position then is that plasma and blood transfusion cannot raise the A.H.G. level of a severely affected patient to the normal range. What this treatment can do is to raise the level to the top of the range for mild hæmophiliacs. For many purposes such as the control of spontaneous epistaxis or hæmaturia this may be adequate but for more serious lesions better levels are required. At present higher A.H.G. levels can only be obtained by using animal material.

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The Cold Hæmagglutinin Syndrome

By J. V. Dacie, M.D., F.R.C.P.

(*Department of Pathology* (*Hæmatology*), *Postgraduate Medical School, London*)

The association of chronic hæmolytic anæmia, hæmoglobinuria, Raynaud's phenomena and cold autohæmagglutination form a syndrome which, although uncommon, is of great interest. I shall refer to it as the "Cold Hæmagglutinin Syndrome".

Cold agglutinins are formed in high concentrations in the serum of man in three main types of disease: (1) after virus pneumonia; (2) in association with hæmolytic anæmia

accompanying reticulosarcoma and allied lymphomas; and (3) in "idiopathic" acquired hæmolytic anæmia of the cold-antibody type. Patients presenting symptoms of the cold hæmagglutinin syndrome belong to this last group. In addition, cold agglutinins at abnormally high titres have been reported from time to time in a wide variety of disorders, ranging from liver disease to trypanosomiasis, but such reports mostly lack details of titres, &c., and one is not always sure whether the auto-agglutination is due to the presence of cold agglutinins or excessive rouleaux formation. The incidence of cold agglutinins at raised titres in what may be termed "miscellaneous disorders" is in any case low. Finland and his colleagues (1945), for instance, studied 809 sera from patients suffering from a variety of disorders, mainly infections, and found only nine sera containing cold agglutinins at titres exceeding 80, and even so, four of these sera came from patients with hæmolytic anæmia.

I shall discuss acquired hæmolytic anæmias of the cold-antibody type, of unknown origin, and those patients whose serum contains cold antibodies at titres in excess of 8,000 at 2–4° C., for these are the patients who present the symptoms of the cold hæmagglutinin syndrome. The first well-documented reports of this syndrome date from 1935. In that year Roth and Ernstene, and Gardner, in America, and Salén in Sweden, all described patients thought to be suffering from paroxysmal hæmoglobinuria, who in retrospect clearly were suffering from the syndrome under discussion.

The incidence of this type of hæmolytic anæmia is illustrated in Table I. The data comprise patients with acquired hæmolytic anæmia personally studied during the last ten years.

TABLE I.—A CLASSIFICATION OF 113 PATIENTS WITH ACQUIRED (AUTO-IMMUNE) HÆMOLYTIC ANÆMIA

Clinical Type	Ætiology	Serology (Type of antibody)	No. of patients
Idiopathic (Acute transient or chronic)	Unknown	Warm	67 patients
		Cold	15 patients
Secondary:			
Transient	Post-virus pneumonia	Cold	12 patients
Chronic	Reticulosarcoma, lymphosarcoma, chronic lymphatic leukæmia, other leukæmias, lymphadenoma	Warm	11 patients
		Cold	5 patients
	Disseminated lupus erythematosus	Warm	3 patients

Of the 15 patients with cold auto-antibodies, 10 were diagnosed as having the cold-hæmagglutinin syndrome, for they all suffered from well-marked Raynaud's phenomena, with or without hæmoglobinuria, in cold weather. (The other 5 patients were relatively free or completely free from these symptoms; they differed also in serological findings.)

The 10 patients with the cold hæmagglutinin syndrome make an interesting series. Some clinical data are shown in Table II. The disease clearly affects elderly subjects and is of long duration; both sexes are affected.

TABLE II.—SOME CLINICAL DATA ON PATIENTS WITH THE COLD HÆMAGGLUTININ SYNDROME

Case No.	Sex	Age	Duration of disease or cause of death
1	F	61	16 yrs. Died of anæmia
2	M	78	1 yr. Died of bronchopneumonia
3	F	67	10 yrs. +
4	F	75	4 yrs. Died of ca. pancreas
5	M	71	3 yrs. +
6	F	73	3 yrs. +
7	F	72	2½ yrs. +
8	F	60	3 yrs. +
9	M	62	"Years"
10	F	68	4 yrs. +

Data on 23 other patients in literature (15 men; 8 women).
Age range: 38–81 years. Mean age 61 years.

The patients suffer from a mild to moderately severe hæmolytic anæmia. Some hæmatological data are shown in Table III.

TABLE III.—HÆMATOLOGICAL DATA ON TWO PATIENTS WITH THE COLD HÆMAGGLUTININ SYNDROME

Red cell count (mill./c.mm.)	Hb (g./100 ml.)	M.C.V. (c.μ.) (mean)	M.C.H.C. (%) (mean)	Retics. (%)	Leucocytes (/c.mm.)	Platelets (/c.mm.)	Serum bilirubin (mg./100 ml.)
(Case 3. 8 yrs.) 2·3–5·0	6·5–14·8*	106	31·7	0·6–16	3,000–11,000	170,000–300,000	0·3–1·8
(Case 4. 3½ years. Died 1954) 1·8–4·2	6·2–14·2†	109	34	2–16	1,800–8,000	50,000–150,000	0·3–2·5

*Summer 1949. †Summer 1951.

The patients are usually significantly more anæmic in winter-time than in warm weather, but they are rarely completely free from anæmia in the summer-time (Fig. 1). If kept in bed their anæmia lessens. This is probably the result of their being kept warm; it incidentally makes assessment of the possible benefit of any other form of therapy unusually difficult (Fig. 2).

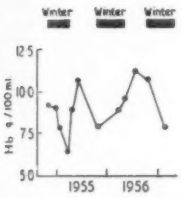


FIG. 1 (*Case 3*).—October 1954–March 1957. Effect of seasons on hæmoglobin levels.

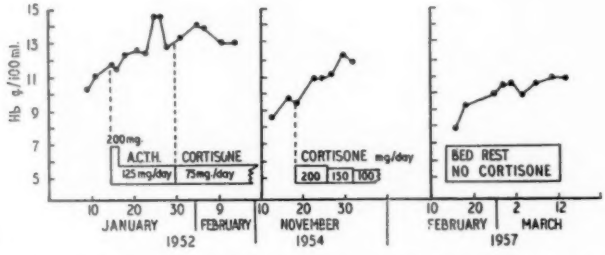


FIG. 2 (*Case 3*).—Effect of bed rest and steroids on hæmoglobin levels.

In cold weather the patients regularly show Raynaud's phenomena. Their fingers feel cold and numb and may be painful, and become bluish-purple in colour. The ear lobes and the tip of the nose may be similarly affected. These changes are quickly reversible on warming the skin, but irreversible changes may occur and gangrene of the tips of the digits is not uncommon.

The circulatory changes appear to be due to auto-hæmagglutination taking place in the cutaneous blood vessels as the direct result of cooling of the skin. As in most cases auto-hæmagglutination takes place at temperatures extending up to 29–31° C., minor degrees of cooling are all that are necessary to bring this about. The cessation of circulation may be readily seen with a skin microscope or by examining the conjunctival blood vessels with the aid of a lens, after having irrigated the eye with cold saline.

Hæmoglobinuria is a less frequently observed symptom than Raynaud's phenomena, but most patients give a history of it at some time during the course of their illness. In some, it regularly occurs every cold winter's day. Even in its absence hæmosiderin may be found in the urine deposit. Most patients, too, are visibly jaundiced in winter-time. Their spleens are usually palpable but are seldom very large.

SEROLOGICAL FINDINGS

Most characteristic is the rapid spontaneous hæmagglutination which takes place at room temperature, making spreading blood films and counting red cells by ordinary techniques difficult or impossible. However, if the blood is collected in a warmed syringe, kept at 37° C. subsequently, and then diluted with warmed diluent and placed in a warm counting chamber, counts are perfectly possible. Similarly, serum free from hæmolysis may be obtained if the patient's blood is allowed to clot undisturbed in a warm vessel at 37° C.

The serological findings in these patients are remarkable. The range of cold-agglutinin titres, and other data, are given in Table IV. Normal red cells are not agglutinated at 37° C. The direct antiglobulin (Coombs) test is positive, even if care is taken to keep the sample of blood strictly at 37° C. before the test is carried out. The indirect antiglobulin test is usually negative at 37° C. but strongly positive if the sensitization is carried out at temperatures below 30° C.

TABLE IV.—SEROLOGICAL DATA IN THE COLD HÆMAGGLUTININ SYNDROME

Cold agglutinin:		
Titre 2–4° C.		8,000–512,000
20° C.		16– 16,000
Upper thermal limit		29–32° C.
Direct antiglobulin (Coombs) test		Positive
Indirect antiglobulin (Coombs) test		Usually negative at 37° C. Positive at <30° C.
Cryoglobulins		Present in 3 out of 10 sera ("Cryocrit" 1·0–5·0%)
Serum complement	*Range* (units)	*Normal range* (units)
	10–90 (3 out of 5 subnormal)	50–150
W.R. and Kahn reactions		Uniformly negative

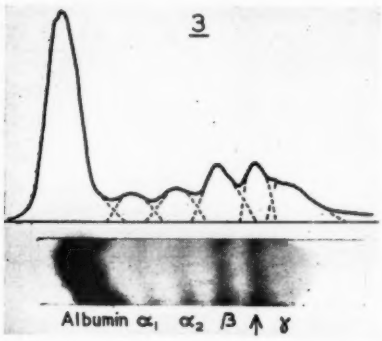


FIG. 3.—Electrophoretic pattern of the serum of Case 3 (agglutinin titre at 4° C. 16,000–64,000). The γ_1 globulin peak is shown by the arrow. From Christenson and Dacie (1957). (Reproduced by permission from the *British Journal of Hæmatology*, **3**, 156.)

Electrophoresis of the patient's sera shows the presence of an abnormal peak in the γ_1 region (Christenson and Dacie, 1957) (Fig. 3). This peak seems to be largely formed of cold-antibody protein. The evidence for this conclusion is as follows (Christenson *et al.*, 1957): (1) If the sera are absorbed with normal red cells the γ_1 peak is removed more or less parallel with the reduction in cold-antibody titre; (2) if the sera are subjected to cellulose-column electrophoresis the greatest antibody activity is found in the fraction corresponding with the γ_1 peak; (3) such peaks are found apparently invariably when the cold-agglutinin titre exceeds about 8,000 at 2–4° C. They are not found in sera containing cold agglutinins at low titres. Ultracentrifugal studies carried out by Dr. P. A. Charlwood have shown that the cold-antibody protein forming these peaks exists largely in the form of a macroglobulin ($S_{20,w}$ 16·4–18·0) (Christenson *et al.*, 1957). In some patients the γ_1 protein is cold-precipitable, i.e. it exists as a cryoglobulin.

TREATMENT

Primarily, it is a question of keeping the patient warm in winter-time, but how this should be done is beyond the scope of this paper.

Steroids do not seem to be particularly effective and it seems undesirable to start treating the patient with such potentially dangerous drugs, when the treatment, even if beneficial to some extent, will have to be continued for years. The one patient of my series treated with cortisone did not seem to derive much benefit.

Splenectomy has seldom been carried out. Baumgartner (1955) mentions one case in which no benefit resulted, and studies of the spleen uptake of radio-active chromium, carried out on one of my patients by Drs. Hughes-Jones, Lewis and Szur at the Postgraduate Medical School of London, showed an accumulation of chromium in both the liver and spleen which does not suggest that splenectomy would have been particularly effective.

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Section of Psychiatry

President—WILLIAM SARGANT, M.A., F.R.C.P., D.P.M.

[*April* 9, 1957]

Homosexuality in Clinical Practice

By DENIS PARR, M.D., D.P.M.

THE difficulty of defining homosexuality is reflected in a number of neologisms which have been devised to express variations of the same concept. Thus, homo-sociality has been used for social relationships between persons of the same sex, homo-eroticism for love relationships, and homo-genitality for contacts at genital level. In addition, terms such as latent, masked, symbolic, or unconscious homosexuality are sometimes used to describe tendencies or relationships which are neither objectively obvious nor subjectively realized. Such concepts are in the realm of theoretical inferences rather than of clinical phenomena.

In view of these disparities, it is desirable that a working definition should be stated when the subject is discussed. The studies summarized in this paper have been directed to cases where homosexual acts with others at genital level, or desires or impulses to commit such acts, are known to have occurred since puberty.

MATERIAL AND METHODS OF STUDY

The investigation was limited to male psychiatric patients. For data on *incidence*, the following groups were used:

(*a*) Mental Hospital returns for 1956, referring to sexual deviation of any kind as a recorded primary diagnosis, in a total of 24,412 patients.

(*b*) Case records of 608 male patients admitted to Belmont Neurosis Unit (detailed scrutiny).

(*c*) Case records of 721 male patients admitted to the Psychiatric Unit of St. George's Hospital at Wimbledon (detailed scrutiny).

(*d*) 500 male out-patients seen at St. George's Hospital in 1956, using only the diagnostic card index to obtain the incidence of homosexuality as a major part of the initial diagnostic formulation.

(*e*) In a review of 2,550 male patients seen in private consulting practice, the incidence of homosexuality as a major problem was established by Dr. Desmond Curran.

The method of ascertainment was, thus, different in these several groups. In all cases, equivocal statements such as "I believe this man to be a latent homosexual", without supporting evidence, were disregarded.

For *more detailed study*, a selection was made, on the sole criterion of adequacy of documentation, of 100 cases seen privately by Dr. Curran, 50 St. George's out-patients, and 35 St. George's in-patients, all of whom came within the above definition of homosexual. Visits were also made to the Social Rehabilitation Unit at Belmont Hospital where, at community meetings, requests were made for people with sex problems to come for individual review. This group approach produced 39 volunteers, of whom 15 were male homosexuals. These 15 were added to the other selected patients, making a total of 200 cases for detailed study. In all, 50 were seen with research in mind; in the remainder, records taken for clinical purposes were used.

FINDINGS

Fig. 1 shows the recorded incidence of the problem in the five groups described (*a–e*). In the St. George's and private series, the numbers who came because of a criminal charge are also indicated, by solid shading.

The 1,329 in-patient records of St. George's and Belmont were analysed for age and for associated diagnoses. There was a very striking difference in the known incidence in different age groups, which fell steadily from 12% in the under 25's to 1·6% in the over 60's. Table I compares the proportions of cases of homosexuality among 138 psychopathic personalities, 177 schizophrenics, 70 alcoholics (in the addictive sense), and 336 patients suffering from endogenous depression, or depression treated with E.C.T. The apparent differences are not significant on statistical test.

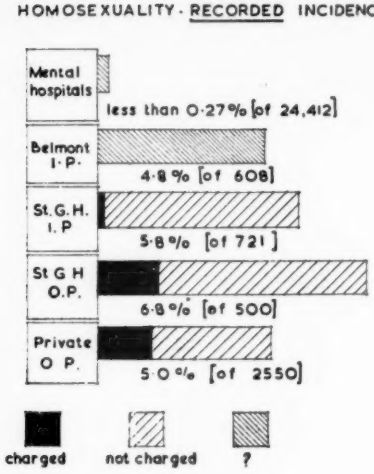


FIG. 1.

TABLE I

INCIDENCE IN DIFFERENT DIAGNOSTIC GROUPS: COMBINED HOSPITAL FIGURES

Diagnostic group	% Incidence of homosexuality
Psychopathic Personality (of 138 cases)	8·7
Schizophrenia (of 177 cases)	6·8
Alcoholism (of 70 cases)	4·3
Depression (Endogenous) (of 336 cases)	3·6
All diagnoses (of 1,329 total cases)	5·3

Estimates of the incidence of homosexuality have ranged from 2% to 100%, it being the view of many psychoanalysts that the condition is universal. For our 1,329 psychiatric male in-patients, the overall incidence was 5·3%. This is undoubtedly an underestimate. Apart from the difficulties already mentioned, there is a further special obstacle to ascertainment. It is a regrettable fact that none of us can guarantee a patient permanent and unconditional secrecy in respect of case notes. There is no knowing, for example, whether at some future date somebody, not necessarily ourselves, may be subpœnaed to reveal every detail of a case history in a court of law. For this reason, some doctors feel that it is wrong, unless clinically essential, to leave written records of criminal sexual practices in hospital files. In countries where security probes are more highly developed, the problem of documentation must be difficult and painful for the doctor.

Fig. 2 gives an indication of the age distribution and occupational groups of the 100 hospital and 100 private cases respectively. The age periods are given as decades, and as can be seen, the maximum incidence is in the group 25–35. In the mental hospital figures for 1949–1951 for male sex deviation of any kind as a primary diagnosis, the age distribution among 182 cases is similar. The classification of available criminal figures is somewhat different, but it appears that the highest incidence of detected homosexual crime is in the age group 31–40. As to occupational groups, the histograms on the right show the percentage distribution using the Registrar General's classification of occupations. (I = professional; II = semi-professional; III = skilled; IV = semi-skilled; V = unskilled.) There is a marked difference in the occupational distribution in the private, neurosis hospital and mental hospital groups. This is not in the least surprising in view of the selective economic factors operating, but the small percentage of groups (IV) and (V) who come to psychiatric notice as homosexuals or sex deviates is rather striking. The magistrate and the prison officer see a higher proportion of men from these classes.

In 40 of the 50 in-patients, homosexuality was an incidental finding only and had no part in determining admission. In the 150 out-patients, the most common reasons for referral were: criminal charge in 39 cases, anxiety over homosexual feelings in 38, various apparently non-sexual problems such as depression or excessive drinking in 39. 12 cases, all of them private, were brought by friends or relatives who asked such questions as "Why is he not married?" and 11 came with marital difficulties. Assessment of fitness for teaching was the issue in 2 cases, while one kept an appointment that he had made several months previously while in prison. One homosexual young man came several times ostensibly to seek treatment by proxy for a friend whom we never saw.

It is not worth listing all of the associated psychiatric disorders in detail in view of the complexity of multi-dimensional diagnosis. In the case of the 150 out-patients, abnormalities found consisted very predominantly in personality problems or neurotic illness rather than psychoses. 17 of the 150 were sociopathic by other criteria. 68 of the 150 were free from gross personality disorder, neurosis or psychosis during their adult lives. This may be thought a high percentage considering that all of these patients came for psychiatric attention. The

Age and occupational status of 100 neurosis hospital, 100 private and 182 mental hospital cases

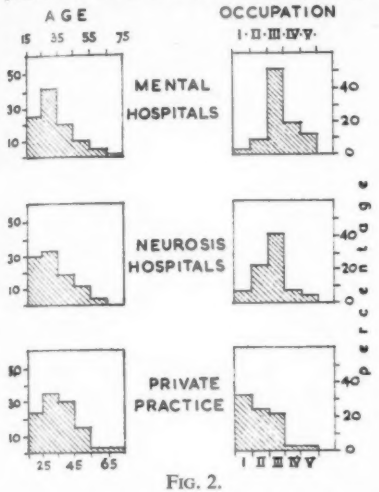


FIG. 2.

reason is that so many came because of a criminal charge or transient situational problems. I think also that many homosexuals reach a stage of wanting medical confirmation of their own belief that they are irretrievably homosexual, so that they can feel free to go on practising for the rest of their lives. When in-patients were included, out of the whole series of 200 one was defective, two dull, three demented and three certifiably insane.

All but 23 of the 200 admitted to one or more acts with others since puberty. Where information on frequency was available, it was possible to make a very conservative estimate that the practising cases committed at least seventeen criminal acts a year each. Of the practising 177, buggery was noted in 42% and fellatio in 24%. In 50 cases about whom better quality information was available because they had been seen for research purposes, the corresponding figures were 62% for buggery and 50% for fellatio. The more we see of these cases the more we incline to the view that there are few regularly practising homosexuals who do not try all variety of acts at one time or another. In the private series of 100, it was found (Curran and Parr, 1957) that those known to practise buggery differed from the remainder of the group only in having a higher level of promiscuity. This finding was confirmed in the larger series including hospital cases.

On the subject of passive or active preference, although many individuals seemed to prefer one role to the other, the majority had practised both at different times, and some were predominantly passive at one time in their lives and predominantly active at another. The exclusive passivity of one man who could masturbate only by means of a candle inserted *per rectum* was, in our experience, unique.

Mechanical details of this nature are of less clinical importance than the preferred age of the sexual partner. Pædophiliacs, meaning those with impulses towards prepubertal boys, are rather a distinct problem. Of the 200 patients studied, 29 had pædophiliac impulses at one time or another. Only 4 had at different times in their lives committed homosexual acts with adult men and with prepubertal boys. The overlap between pædophiliacs and adult-seekers, as they may be called, was therefore very small. Between those active with boys aged 14 to 16 and those active with younger or older age groups it was considerably larger. There was no evidence of any tendency for homosexuals preferring adults subsequently to commit acts with young boys—the so-called "Rake's Progress".

Significantly more of the pædophiliacs than of the remainder of the series were bisexual. The practising pædophiliacs showed a rather remarkable capacity for self-deception and self-righteousness. The special problem of the pædophiliac is, in my opinion, aggravated by the fact that he has no group affiliations in his sex life. Homosexual society differentiates and acknowledges many of its practising members with such titles as Duchesses, Queens, Cows, Bitches, Butches, and Butch-renters, but so far as I have been able to discover, there is no name for the pædophiliac.[1] He is disapproved of and rejected by the homosexual world as by the world in general, and is obliged to be a furtive lone-wolf in his sexual pursuits.

Sexual perversions other than homosexuality were noted in 30 of the 200 cases, the incidence being higher in the hospital than in the private groups. Some psychopaths admitted to experimental indulgence throughout the whole range of sexual deviation, when as normal and neurotic men were less polymorphous in these respects.

In general the series was highly promiscuous. For example, in 51 cases where relevant information was noted, the median number of homosexual partners admitted was 12 and the mean 38. Of the 200, 35 specifically admitted to acts in public lavatories, affectionately known as "cottages" in the parlance of the queer world.

It is sometimes claimed that promiscuity, as opposed to fidelity, in homosexual relationships is in itself a symptom of associated psychiatric disorder. This is an attractive thesis, particularly in relation to psychotherapy, but we have not been able to confirm it in our series. Indeed, on comparing the psychiatrically normal homosexuals with the remainder

[1] The author has since learnt from conversations during a WHO study tour that the same is true of homosexual society in Sweden.

of the series—or, if preferred, the less abnormal with the more abnormal—the reverse is found to be true. Significantly more, at the 5% level of probability, of the less abnormal sub-group admitted to 6 or more partners. Nor have we been able to confirm Henry and Gross's (1938) finding that underprivileged homosexuals are more promiscuous than the more favoured economic groups. Comparing Groups I and II with the remainder of the combined series reveals no significant difference in this respect.

In regard to civil status, 37 of the 200 cases were married. The mean age at marriage was 27·3, which is the same as the national average. Two-thirds of those who married did so before the age of 30. As many married women younger than themselves as married older women, the mean age difference being 0·3 year older than the wife, as against the national average of three years older. Some almost completely homosexual men claimed normal technical performance in intercourse. The subject of married homosexuals deserves special study, but unfortunately case material is all too hard to find.

No significant difference was detected in the psychosexual experiences in early or later life of the grammar and public school boys, who constituted respectively 20% and 35% of the whole series. It is probable that the significance of segregated or boarding school education as a contributory factor in homosexuality has been greatly exaggerated. Adult homosexuality may occur in spite of co-education at all stages of childhood and adolescence. In view of the facts that the vast majority of the population is educated at State day schools, and that many, if not most, of such schools are co-educational, it is surprising that the myth of segregated education as the principal cause of homosexuality has been so long sustained.

For reasons discussed in a previous publication, we believe the Kinsey Scale to be a most valuable classification. In these 200 patients, the Kinsey rating was often not used at the time, but the majority were classified as 100% homosexual, bisexual-predominantly homosexual, bisexual-predominantly heterosexual, or simply as bisexual. 83, that is 41·5% of the whole series, were classified as Kinsey 5 or 6 or as 100% homosexual or nearly so, and the proportions in the private and hospital series so diagnosed were practically the same.

In regard to the controversial question of early seduction and its effects, we have found no significant association within the series between a history of seduction and a tendency to pædophilia in adult life. The finding in the private series that seduction was reported more often by those on a criminal charge than by those not on a charge was not confirmed in the hospital series. In a retrospective survey (made by P.S.W. colleagues) of 100 consecutive male referrals to the St. George's Hospital Child Guidance Clinic, the number referred because of alleged seduction was 3, while seduction was an incidental finding in another 3. In none of these cases, so far as could be ascertained, was the event a major causal factor in the child's psychiatric disturbance.

The recent work of Garrone and Mutrux (1956) in Geneva reminds us that the investigation of sexual deviation on physical lines has, to date, been notably unrewarding. We have little to contribute in this connexion. Laboratory examination of semen by Dr. G. I. M. Swyer and sexing of polymorphonuclear blood cells by Dr. J. L. Stafford have been carried out in a few cases, so far with normal findings.

So far as the clinical data are concerned, our findings need to be interpreted with great caution in view of the nature and size of the sample. On the other hand, comparison of private patients with hospital patients, and of out-patients with in-patients, has revealed few important discrepancies in the main findings.

Having begun by deprecating the surfeit of speculation in the literature on homosexuality, I should like to end with some highly speculative arithmetic.

If the incidence of homosexuality in different age groups in the male population of England and Wales was the same as in the groups of in-patients we have studied, and if the average figure of fifteen criminal acts a year each applied to all these homosexuals, then the ratio of criminal acts to known indictable homosexual crime would be of the order of 2,500 to one. To take another series of assumptions, if the Kinsey findings were true of England and Wales, then within the age group 21 to 30 only, this ratio would be 30,000 to one.

Such fanciful figures may be of little more than journalistic value. Their exact validity, however, is less important than the fact that there is an almost astronomical disparity between the numbers of illicit sexual acts that occur, and those that are detected and prosecuted by the guardians of the Law. Perhaps on this point—if on no other—we can all agree.

ACKNOWLEDGMENTS

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Homosexuality, with Special Reference to Classification

By P. D. Scott, M.A., M.D., D.P.M.

The first impulse towards the study and classification of homosexuality as a clinical entity came from K. H. Ulrich, a legal official in Hanover in the middle of the last century. Himself sexually inverted, it is characteristic that he should have viewed the matter in two colours only; to him an individual was either an urning or a dioning and had been born that way. Subsequent investigators, accepting the plausible opinions of their patients and perhaps believing that only an inborn condition could be so resistant to treatment, persistently included in their classifications of homosexuality a "congenital" group. Many, perhaps most, psychiatrists continue to do so to-day.

In addition to his congenital group, however, Krafft Ebing (1883) recognized the outstanding clinical fact that some homosexuals have circumscribed sex perversion while others have their whole personality coloured in harmony. Schwarz, on the one hand, said that "Serious perversions are imbedded like a foreign body within a completely normal personality", while Karen Horney, on the other, maintained that character explains perversion and that sex disturbances are the effects not the causes of neurosis. This new approach had been made possible through Freudian teaching which, in essence, postulates an original and basic freedom of choice of love object and that the homosexual's choice is limited by dominance of castration fears. Ferenczi introduced two new categories, the subject-homo-erotics (more narcissistic than feminine, behaving as the subject wished his mother had behaved to him) and the object-homo-erotics (anal rather than phallic characters, wishing to enjoy sex in the same way as mother, tending to submit themselves to father figures). While these active-passive homosexual, and subject-object homo-erotic categories have real clinical significance, their usefulness is diminished by the fact, recognized by Freud and others, that the forms are commonly mixed or successive to one another.

Kinsey's work removed the concept of a third, intermediate, sex. There are hazards, however, in using for clinical purposes what were purely research categories. Placement of an individual in one of Kinsey's six grades must be highly subjective; Kinsey himself had to abandon his neat definition of homosexuality for this purpose and considered "both psychologic reactions and overt experience". Doctors tend to see mainly those in grades 5 and 6. Position on the scale does not indicate absolute frequency, force of drive, "compulsiveness", whether the homosexuality is a matter of phantasy or action. Bisexual as well as homosexual and, indeed, heterosexual persons may become recidivist sex-offenders. Conversely, an apparently totally homosexual person may be facultative in the sense of being able to respond to environmental changes, of being adaptable, of lacking a strong compulsive drive to one form of sexual behaviour. Especially where there has been long segregation in communities of one sex, or if at the time of examination the individual is living in such a community, then, even if homosexual behaviour is habitual and exclusive, there should be caution in assuming that it is irreversible. It would be reasonable to postulate two variants. One concerning choice of object (homosexual, heterosexual, &c.) and the other concerning the freedom or rigidity with which this choice is expressed (facultative, "compulsive"). In many bisexual cases there is very much less real freedom of sexual expression than at first sight appears.

Dramatic changes in mode of sexual expression are commonly observed and only serve to underline how much homosexuality is a complex adaptation as distinct from entirely an inherent tendency.

Rado describes Variational, Situational and Reparative patterns of sexual behaviour. The reparative patterns are means, largely unconscious, of circumventing early fears. He points out that these reparative patterns are highly inflexible and that the individual depends upon them for full orgastic gratification in all circumstances. He states also that such an individual cannot gain real satisfaction from standard sexual performance, evidently not accepting that some individuals are so successful in their adjustment that they are frequently able to enjoy heterosexuality provided they pay for it in the appropriate manner. His approach like that of Boss and other existentialists makes for a classification of all sexual activity rather than for a limited classification of homosexuality alone.

Equally broad and even more clinically applicable is Mangus' classification of sexual deviations—non-pathologic, subcultural and pathologic deviations. The latter he divides into seven degrees taking into account the degree to which the tendency is abnormal, the strength with which it is expressed and controlled, and the extent to which it is dangerous or embarrassing to others. It is broad classifications such as this which prevent the not

infrequent confusion of, say, homosexual play in childhood and adolescence, with reparative patterns seen in clinics, or with so-called homosexuality in ancient Greece or in isolated island communities. It is fair to state that these conditions are utterly unlike and that conclusions based on one group are by no means applicable to others.

For completeness the concept of pseudo-homosexuality, which appears in many classifications, needs comment. Some writers describe as many as twelve different forms of pseudo—or spurious—homosexuality. This throws much light on the psychopathology of homosexuality but is not really useful for classification purposes, for all homosexuality is spurious or counterfeit sex, and the personality has always to be taken into account. Since the quality of the personality seems to be of major importance in matters of prognosis and treatment the following groups (recognized as arbitrary sections from a continuum) were defined as seeming to represent the male homosexual material seen in hospital clinics, prisons and remand homes:

A. *Adolescents and mentally immature adults* sometimes go through a phase in which they are uncomfortably aware of their attraction to both sexes and do not know how to resolve their quandary. Some seem to settle in favour of heterosexuality and have no further trouble, others become homosexual or manage to become stable bachelors. In any event they are much in need of supportive psychiatric treatment and perhaps of psychoanalysis. They are not socially dangerous.

B. *Severely damaged personalities:*

(1) The very effeminate, self-advertising, female-impersonating individual who talks in an affected manner, walks with a mincing gait, wears make-up and frilly underclothes. Most of these are sexually self-sufficient but, needing to be acclaimed by others, they enjoy the chase rather than actual sexual contact, though they may become homosexual prostitutes. Most homosexuals avoid these persons unless for want of more satisfying partners. They are not socially dangerous.

If young, and they usually are, they are best placed in a hostel, but it must be one in which the warden is familiar with the problem. Many lay-people consider that such youngsters will demoralize the community. But if handled calmly and given a homely atmosphere they settle readily and harmlessly. Psychological treatment as opposed to psychologically inspired handling, does not seem to be successful.

(2) The inadequate, down-trodden, dull (whatever the I.Q.) who have never experienced a loving relationship with anyone and are almost socially isolated. They tend to snatch fleeting contacts in lavatories sometimes for payment, are not socially dangerous and are likely to be untreatable in the clinic. They are most likely to respond to very long-term supportive treatment from a probation officer or other social worker. Ideally they should be accommodated in special communities for those who cannot cope with ordinary social requirements.

(3) The deeply resentful, antisocially inclined individual usually with a long record of court appearances, starting in childhood with Truancy and Beyond Control charges. They tend to come from homes in which the mother is at the same time possessive and hostile to the boy. It is difficult to determine to what extent they really are homosexual, for they are ready to exploit anyone and anything. Socially they are dangerous to other homosexuals whom they victimize and to society through their non-sexual offences. They seem to disappear from clinics after the 20's, perhaps to prison. No treatment method has been shown to be effective.

C. *Homosexuality in relatively intact personalities* who are quite well socialized. This group includes the youths who have digested scruples and are living pleasurably, often under the patronage of older homosexuals of the same sort. Such individuals soon learn the ropes, rarely approach anyone before they are sure that it is safe. These people are happy, are able to hold useful jobs. They support one another. They are not at all socially dangerous. They do not want treatment and it should not be forced. A sympathetic attitude with explanation of the particular risks they run at time of emotional stress, is often worth while and all that is necessary. If they have been handled tactfully they will, and do, come back.

In this division also are the less happy individuals who are unlucky enough to be bound to socially more difficult love objects such as children, so that there can be no support from the minority group for them. These, of course, may be a danger to children. They benefit with psychiatric treatment and some psychotherapists are optimistic about helping if not curing them. They may also respond to probationary supervision in controlling if not in radically changing their sexual preference.

D. *Latent and well-compensated homosexuals.*—These are often men of considerable strength of character who may not appear in court or clinic until late in life. They either genuinely do not know what their real difficulty is or else have struggled in the main successfully against it. Very often they are intelligent, perhaps married with healthy children, perhaps teachers, business directors, youth workers. They are particularly at risk during times of additional stress or during the depressions of later life. They are also particularly likely to carry out one of the symbolic or "incomplete" offences, touching, fondling, exhibiting in lavatories. Unfortunately children are often involved but are always treated gently and are probably already predisposed to such approaches. They usually soon regain their poise and should then be kept under occasional observation through a supportive clinic. They may perhaps be tided over further danger periods by means of closer support, together with sexual sedatives (œstrogens). It is this group which stands to lose so much through imprisonment. Those who are so unfortunate will be very much in need of rehabilitation afterwards.

E. *Homosexuality coexisting with serious mental disability.*—This ill-defined group includes those with psychoses, organic brain damage and the extremes of personality defects. They are, of course, very dangerous socially. They are apt to injure their victims in a way which none of the others would contemplate, nor do they take only "predisposed" victims. They have to be segregated till rendered harmless by ageing or specific treatment. Actual punishment is, however, probably less useful here than in any of the categories. Section 8 of the M.D. Act 1913 or admission to a mental hospital may be indicated. This is the group which presumably should be accommodated in an East-Hubert prison-hospital.

With the help of colleagues at the Maudsley and Bethlem Royal hospitals, all the cases diagnosed as homosexual in the two hospitals during 1951 and 1952 were analysed in certain respects. There were 72, 63 males and 9 females.

Preferred Sex Object	M.	F.
Child	11	—
Young person	10	1
Adult	32	7
Variable	5	—
Not known	5	—

Social Threat	M.	F.
Harmless	37	7
Nuisance	14	2
Dangerous	9	—
Not known	3	—

Preferred Activity (Male)	
Phantasy only	4
Masturbation with partner	27
Sodomy	18
Intercrural	2
Not known	12

		M.	F.
A.	Adolescent-like conflict	10	3
B.	Severely damaged personality		
	1. Very effeminate	3	—
	2. Inadequate	15	1
	3. Antisocial	6	1
C.	Well socialized, accepting homosexuality	13	1
D.	Latent and well compensated	3	1
E.	With serious mental disablement	6	2
	Doubtful	7	

Kinsey Group	M.	F.
1	4	
2	4	
3	2	
4	8	2
5	21	2
6	22	4
Not known	2	1

A fertile field for research would seem to be the comparison of homosexuals with other selected samples, in respect of personality and family background. It has several times been stated that homosexuals are more intelligent than other sex offenders, and certainly they give the clinical impression of being in the main better integrated persons. The following assessments of social class and occupational grade with different samples of homosexuals confirms the general direction of this suggestion. The average ages of the homosexuals and exhibitionists were 34 and 31 respectively.

SOCIAL CLASS DISTRIBUTION (MALES OVER 15)
ACCORDING TO THE REGISTRAR GENERAL'S CLASSIFICATION

Social class	Greater London Conurbation 1951 Census (2,904,849) %	London exhibitionists 100 hosp. pts. %	26 prison convicts %	London homosexuals 100 hosp. pts. %	40 prison convicts %
1	4·6	0	0	2	2·5
2	16·2	4	4	16	22·5
3	55·2	68	58	60	42·5
4	10·7	19	23	19	22·5
5	13·3	9	16	3	10

Similar findings were demonstrated using the Hall and Jones Scale.

The psychoanalysts state that there is no specific homosexual ego, and clinical experience reveals no specific personality type, yet certain features occur so frequently as to suggest a linkage of common causation. The inability to reconcile dependent and assertive drives seems especially common. However able, they sometimes feel paralysed when instructed or expected to carry out a task, even though it be well within their capacity. Associated with this is their common complaint, more marked than in any other sort of patient, of procrastination.

The early belief that the child failed to develop emotional independence from his mother because of her over-gratification of his needs, has now generally been abandoned in favour of the opposite view, expressed by Fenichel—"children in general tend to identify themselves more with the parent from whom they have experienced the more impressive frustrations".

The descriptions of mother as given spontaneously by 36 homosexual patients and 36 controls (neurotic and psychotic) were classified under seven headings and compared. Approximately two-thirds of each used terms implying good, positive qualities, yet terms implying dominance and negative qualities were nearly twice as frequent in the homosexuals, implying that an ambivalent relationship is commoner in homosexuals.

Impressive frustration in the childhood of homosexuals is certainly the rule. Considering the incidence of broken homes it was found that of a group of 40 convicted homosexuals serving short sentences, one-third came from actual broken homes (one parent absent). All but 3 of the cases showed gross and acknowledged emotional disturbances in their early family life. In a series of 20 juvenile homosexual offenders, half the homes were "broken" and all but 2 showed gross emotional disturbance.

In an attempt to ascertain significant questions for the study of the backgrounds of homosexual patients, Dr. N. H. Rathod and I put a series of 197 questions to 15 homosexual patients and to 15 neurotic or recovered psychotic controls not suffering from sexual disorders. The following composite case history includes the most significant points:

> The patient is a male in his early thirties. His father is likely to be recently dead. Father was much older than mother:
>
> | | Parental age-discrepancy 5 or more years | 10 or more years | 15 or more years |
> |---|---|---|---|
> | Controls | 5 | 3 | — |
> | Homosexuals | 7 | 5 | 4 |
>
> Father is described by the patient in predominantly negative terms. He does not conceal his dislike for his father. Strict, disinterested and jealous are common terms used in describing him. Father himself was brought up strictly. Mother is alive and aged about 59. She is described as a good mother but also as determined, capable, forceful. She is not criticized freely by the patient but he indicates ambivalence to her. Very frequently he either describes his difficulty in showing affection to her, or she to him. She goes out to work and enjoys doing so. She works or has worked as a manageress, teacher, nurse or artist. She worked when the patient was a child, in many cases between the time he was 2 and 6. Mother's marriage was not "forced" by pregnancy. She wanted a boy, yet when she had one often treated him like a girl. Mother is more likely to have been the only child or youngest of her family. She had most feeling for her father, but broke off relationships with her home early. She tends to look down on men. There is no particular tendency to mental disorder on either side of the family. This patient comes toward the younger end of the family. His male siblings have more celibacy or broken marriages. Discipline at home is strict but not necessarily consistent. The patient does not feel rejected. Mother imposes discipline more frequently than father. The patient has often been fussed and

over-protected. In arguments mother gives in less frequently than father. Almost invariably the patient used to avoid fights and rough games. Apart from nail-biting, tics and masturbating, there is no marked tendency to the so-called neurotic traits or behaviour disorders. He did not especially frequently play truant, or bed-wet, or have marked fears. He was, in general, conforming and he helped his mother greatly. Tendencies to dressing-up, amateur dramatics, feminine occupations, playing exclusively with girls before puberty, were surprisingly not especially common. He got on better with adults than with young people. He did not want to be like his father. He was much aware of inferiority feelings as a child. His awareness of sexual feelings was early but the onset of puberty was not.

	First awareness of sexual feelings					Av. onset of puberty (Years)
Age in years	0–5	6–10	11–15	16–20		
Controls	—	4	7	3	Controls	14
Homosexuals	4	4	5	1	Homosexuals	14



FIG. 1.

Finally, Fig. 1 epitomizes much of the homosexual's problem. It is of a 4½-year-old boy, now an actor in his fifties, Kinsey grade 6. He is wearing a red velvet dress, his hair is dressed with macassar oil and done up in a bun; though difficult to see in the photograph he is wearing a bangle and a large ring; he carries, of all things, a whip. Even in those days it was quite exceptional to treat a boy in this way at 4½. Mother was described as "deeply religious and very, very strict". Father was twelve years older than mother and died young. Most of this boy's upbringing was left to unwilling older sisters of whom there were six. He is the only boy and youngest child. A constellation of circumstances more certain to produce sexual disorder of some sort could not have been devised; the most superficial investigation by a social worker could surely have recognized his peril. No preventive action was taken and, furthermore, despite the considerable advance in knowledge, it is scarcely any more likely that preventive action would be taken in similar circumstances to-day—half a century later. The irony of the matter is that though he did not rebel then, he has spent the rest of his life rebelling in the sexual field and otherwise, and though he was probably unhappier then than he is now, it is to those days and to that red velvet dress, that he has always wanted to get back. It is also to that age group that we should be looking for the answers to questions of causation and prevention of crime and sexual maladjustment alike.

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Dr. I. C. N. Gibbens:

One of the main conclusions we can draw from this discussion is that there are many types of homosexuality and that many apparent differences of opinion may be due to people talking about different types as if they were one. My own experience has recently been with yet another type—the ordinary offender, usually thief or house-breaker, who happens to be homosexual. Recently, I examined every other lad (aged 16–21) sentenced to Borstal training in the Greater London area,

comprising a total of 200 lads. None of them was sent to Borstal for a homosexual offence or had ever been convicted of one. All of them are being seen again in Borstal a year later; since this has been carried out in the first hundred, and forms some sort of check, I shall refer mainly to them. The incidence of homosexuality was similar to estimates which have just been given. 3% were homosexual prostitutes (convicted of larceny or robbery) who talked about their inclinations freely. A further 13%—making a total of 16%—were considered to have important homosexual problems which might complicate training, although they denied any inclinations. Two were later shown to have withheld information about strong tendencies, but many of the others were suspect because they were uninterested or undecided in the direction of their interest. After following them up, it seemed that the best pointers were hostility to girls, a fear of being "bossed", or cheated by them; and an unexplained conviction that they would never marry. When seen a year later, the prostitutes had not given much trouble, and one of the others had been sent to prison for a serious offence. Again, 13% of the lads—unfortunately, not very often the same lads—had had to be dealt with for homosexual behaviour; usually of a minor kind but never an isolated event. A total of 15% therefore either showed homosexual behaviour or had declared inclinations. The figures for the second hundred were similar—5% with definite inclinations and 20% "suspects". When the suspects were contrasted with the remainder in respect of 94 objective factors in criminal and social history, the statistically significant differences were that the suspects had had neurotic symptoms and psychiatric treatment more often, and, rather curiously, that they practically never had a major physical disability. Physical defects do seem to be common in other types of sexual deviant.

The most interesting information produced by these lads, however, referred to seduction. During examination of the first hundred it became clear that many had been sexually approached by adult men, though this was often not mentioned since an experience of this sort was not considered to be related in any way to discussion about homosexual experiences at school, &c. The second hundred were asked systematically whether an adult had ever "made a pass at them": no less than 34% remembered at least one incident of this sort. Usually "a man in a cinema once put his hand in my lap": less often money had been offered in some alley-way. The interesting thing was the proportion reporting this was precisely the same whether the boy was a "suspect" or not—34%. The ordinary heterosexual boy clearly thought it of no significance and not worth mentioning in reference to his sex experiences. 8% had suffered some actual seduction; the unusual feature was that there had been a response, though some had had experience with contemporaries before and the incident only taught them that it could be financially profitable.

Little has been said about physical factors in homosexuality. I believe that these undoubtedly exist, but, again, the lack of satisfactory classification of homosexuals has prevented progress. The first one hundred were asked to agree to measurement and anthropometric photography after the manner described by Sheldon, but with the improved technique of Tanner (1951). Only 56 lads consented, and the material bearing on homosexuality is, therefore, small. As a whole, the Borstal lads were markedly mesomorphic (muscular) in somatotype. In the "suspect" group the two main characteristics were:

(1) That the extreme in each dimension—in endomorphy, mesomorphy and ectomorphy—was a definite homosexual.

(2) Pronounced endomorphy is uncommon in delinquents, and 3 of the 5 examples were suspects.

(3) The characteristic physique of the "undecided" and undifferentiated suspects was mesopenia, or lack of muscle: they looked and were rather feeble youths.

From the institutional point of view these lads fall into roughly four groups:

(1) 3% of prostitutes or others of declared inclination who are in some ways the least difficult to manage, though their response to training is problematical.

(2) 2% of older neurotic lads with strong but concealed inclinations. These are the most difficult since they are liable to emotional upheavals without notice.

These two groups are the more serious homosexuals. The remainder are composed of:

(3) 5% of rather aggressive and criminally sophisticated youths: they have strong heterosexual interest, though often with much conflict, and their activities are partly a substitute.

(4) 5% of immature undecided lads whose activity is of the common schoolboy type.

I should like to add that to an outside observer like myself the method of dealing with cases in Borstal seems to be tactful and humane, protecting the individual from undue influence, but not depriving the homosexual outright of a chance of benefiting from training.

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Section of Neurology

President—D. W. C. NORTHFIELD, M.S., F.R.C.S.

[*March* 7, 1957]

MEETING AT THE WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, LONDON

The following cases were shown:

Kalodent Spinal Grafting for Lumbar Retrolisthesis.—Mr. GEOFFREY KNIGHT.

(1) Internal Carotid Stenosis (Atheromatous). (2) Internal Carotid Stenosis (Traumatic). (3) Internal Carotid Stenosis (Atheromatous).—Dr. COLIN EDWARDS.

(1) High Cervical and Lumbar Syringomyelia. (2) Rapidly Growing Multiple Schwannomata.—Dr. T. ROWLAND HILL.

Aneurysm Right Middle Cerebral Artery. Recurrent Spontaneous Intracranial Hæmorrhage with Intracerebral Hæmatoma.—Mr. CAMPBELL CONNOLLY.

Ocular and Neurological Manifestations of Mumps Encephalitis.—Mr. J. MINTON.

Intracranial Hypertension with Early Loss of Vision.—Dr. JOHN MILNES.

[*April* 4, 1957]

DISCUSSION ON DISORDERS OF THE HIND-BRAIN CIRCULATION

Mr. John M. Potter (University Department of Neurosurgery, Manchester Royal Infirmary):

Arterial Blood Flow Patterns

The cerebral circulation via the vertebral arteries has received much less attention than the circulation via the carotids: because the latter are so much more easily accessible before and after death, they have received a disproportionate amount of attention.

Nearly ten years ago, we (McDonald and Potter, 1951) were attracted to the vertebral-basilar system which in the rabbit—the experimental animal that we used—is similar to but relatively more pronounced than that of man. But we were soon distracted from the cerebral circulation itself by the discovery that the blood flow in the basilar artery was laminar or streamline in type; rather than a truly turbulent (or hydraulic) flow in which the components of a fluid follow random pathways and which is wasteful of energy. That streamline flow occurs in veins has been known for many years, but the ready opportunity for observing whether or not it is present also in an artery does not arise until one is able to see two arteries joining to form another, and this is the unique feature of the usual type of vertebral-basilar junction. Moreover, in the rabbit, these arteries are sufficiently translucent to see what goes on within them.

Thomas Willis (1684), in referring to the anatomy of the brain, said that "in other parts where matters appear to the senses we do not so easily fall upon errors", and he thus indicated the general truth that knowledge comes more slowly concerning structures which are well shielded from the cursory investigator. The careful and time-consuming studies of Hutchinson and Yates (1956) have emphasized that we may indeed "fall upon errors" if we consider the cerebral circulation only in terms of the carotid arteries and their patency.

Since Willis's day, the anatomical approach has been a popular one in deducing cerebral circulatory function; but, as in other spheres, it is in itself inadequate, and this is particularly so in the study of arterial anastomoses. An anastomotic artery, it is ordinarily assumed, will have blood passing through it in one direction or the other. But sometimes blood will enter it from either end—and what happens then? We borrowed a term used by Kramer (1942), the "dead point", to describe the interface between the two such opposing columns of blood. I think now that this is an ill-chosen term, for it has a dead, anatomical inadequacy, and misses the essentially dynamic activity that is present at such a point.

[A cine-film: "Blood Streams in the Basilar Artery" was then shown by the author.]

Such evidence as I have suggests that the basic pattern of blood-flow in the rabbit is present also in man, but that in man it is probably modified by the more erratic formation of the vertebral-basilar junction. In the rabbit, the limbs of the Y-shaped junction usually lie symmetrically all in one plane, and I do not recall ever having seen (in some 60 rabbits) a basilar artery that was at all tortuous. These anatomical differences in man should not in themselves produce true turbulence of the bloodstream, but they might affect the course of the individual streams and allow perhaps spiral streams which would give in an arteriogram the appearance of filling the lumen of the basilar artery.

I have examined vertebral arteriograms of 74 patients with an eye for these points. In the first place, some of those films which were relative failures as arteriograms were of considerable interest in other ways. In nearly a quarter of all the arteriograms there was distinct evidence of streamline flow in the basilar artery, and in a third of these it was seen in the *lateral* view. Now, if it is seen in this proportion, it is likely to be the normal state of affairs, for the streams are easily upset, whereas it would be impossible, I think, to create them by injection into an already turbulent bloodstream. Furthermore, the theoretical approach suggests that the threshold for turbulent flow is unlikely to be reached in this artery except perhaps at the peak of systole in a large artery, or when there is a high pulse rate. McDonald (Hale *et al.*, 1955) has, in recent years, been concerned with the complexities that are introduced into this subject by the pulsatile nature of the blood flow, and he has kindly checked on this matter. I have supplied him with measurements taken from the arteriograms, which show a mean internal diameter for the basilar artery of 3·0 mm. with a rare maximum of 5·0 mm. and a minimum value of 1·7 mm.

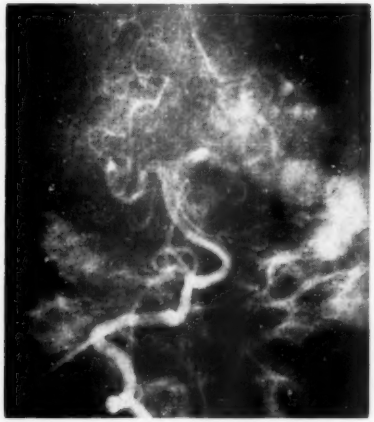


FIG. 1.—Rt. vertebral arteriogram, showing streamline flow in a large basilar artery.

Velocities of flow have to be guessed for man by analogy with animals in which they are known. A high velocity makes for instability of the streams, but it is of interest that one of the best arteriograms showing streamline flow (Fig. 1) is seen in a case of an arteriovenous malformation where the velocity of flow might be expected to be abnormally high and in which the basilar artery is rather a large one—4·2 mm. in its maximum internal diameter. Sometimes a ghostlike appearance of an artery is seen with sharp contrast medium only where it is clinging to the walls. Flow is slowest there, and the most peripheral laminæ get left behind after the more axial streams have passed on.

Finally, the contrast medium may represent only a portion of the lumen of the artery; that is, only one set of streams is shown. This was striking in one arteriogram, where an apparent difference of one millimetre in the diameter of the basilar artery was seen between that in one film which showed only some of the streams, and that in another where the lumen was fully filled with contrast medium.

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Dr. E. C. Hutchinson (Newcastle, Staffs.):

When the clinical effects of occlusions of the proximal portion of the vertebral artery are considered it is necessary to define the words "proximal portion"—it refers to that part of the artery within the vertebral arterial canal and the part arising from the subclavian arteries. Stenosis or occlusions of this part of the artery play a much larger part in cerebrovascular disease than the relatively rare examples of occlusions of the intradural portion of the vertebral artery. In the 35 patients who died as a direct result of a "cerebral thrombosis" it was later shown that stenosis or occlusion of the cervical portion of the vertebral artery played a part in the final infarction of brain tissue in just over one-third of the patients. In contrast, occlusion of the hind-brain arteries within the skull was present in only 3 patients.

Analysis shows that the vertebral artery, when affected by atheroma in the neck, plays a part in the clinical picture in one of three ways. Firstly, acting alone, stenosis of the cervical portion may cause infarction of the hind-brain; secondly, combined with disease of the carotid artery it may produce a characteristic pattern of infarction of the hind-brain—characteristic in that it affects both the cerebral hemispheres and the cerebellum; thirdly, disease of the vertebral artery may be an important factor in the syndrome of carotid artery occlusion.

The 2 patients with hind-brain infarction due to stenosis of the vertebral artery have been previously described (Hutchinson, E. C., and Yates, P. O. 1957, *Lancet*, i, 2) but it should be noted in this context that the 3 patients with occlusions of individual intracranial hind-brain arteries also showed extensive disease of the vertebral artery in the neck. It may well be that further studies will define a syndrome in the hind-brain, associated with vertebral artery disease, comparable to that seen in the fore-brain with internal carotid thrombosis.

When the cervical portions of the vertebra and carotid arteries are both affected by atheroma the clinical effects are seen in one of two situations. The first occurs as a result of a fall in the systemic blood pressure from various causes. We have seen it in operative shock, Stokes-Adams attacks and carbon monoxide poisoning. Following the episode of hypotension there suddenly develop the signs of an intracranial lesion. The clinical picture is not remarkable, the patient usually being unconscious with a hemiparesis, but the pattern of infarction of the brain is distinctive since both the cerebrum and cerebellum are affected simultaneously. The infarction of the cerebellum, at least, must be attributable to disease of the vertebral artery. The second effect, and this is probably the most important role of the vertebral artery in cerebro-vascular disease, is seen in the syndrome of occlusion of the carotid artery.

One of the most puzzling features of this syndrome has been the mechanisms underlying the recurring episodes of motor and sensory disturbances so frequently seen.

In a series of 13 cases, with adequate clinical and pathological data, the clinical history followed one of two broad patterns. In 7 cases the history consisted of a single episode and this eposide was usually a hemiplegia. The mechanism of the hemiplegia as shown at post-mortem was either occlusion of the middle cerebral artery independent of the diseased carotid or extension of thrombus from the carotid to the middle cerebral artery. In each case the vertebral arteries, and often the other carotid, were free of disease. In contrast there were 6 patients who presented with what may now be called a "classical" history of internal carotid thrombosis. In each of these 6 cases not only were the carotid vessels stenosed or occluded but also the vertebral arteries in the neck were affected to a similar degree. Because of these observations we feel justified in regarding this particular presentation of carotid thrombosis as an expression of failure of the collateral circulation—an important factor in this failure being stenosis or occlusion of the vertebral artery.

Dr. P. O. Yates (Department of Pathology, University of Manchester):

Pathological Changes following Proximal Vertebral Arterial Stenosis

This paper is based on the pathological findings in 100 patients who were selected for particular post-mortem study because they had shown clinical evidence of cerebral ischæmia.

Though I am concerned with the pathological changes following proximal vertebral arterial stenosis, I do not believe that any really valid conclusions can be reached concerning the effects of disease of the vertebral or of the carotid arteries on the brain without a full knowledge of the state of all 4 vessels throughout their course. In these 100 cases, therefore, the whole length of the carotid and vertebral arteries was examined both radiologically and by dissection. This was facilitated by injecting the vessels at post mortem with a radio-opaque gelatin mass consisting of 15% silver iodide in 10% gelatin. The mixture was prepared by adding silver nitrate solution to solution of potassium iodide and gelatin in water. The cervical vertebræ were removed entire, the bone decalcified and the arteries dissected (Fig. 1).

Significant atheromatous stenosis (narrowing of the lumen by half or more, or complete occlusion) was less common in the vertebral arteries (57 vessels) than in the carotid arteries (77 vessels). In 5 cases both an internal carotid and a vertebral artery were occluded, this being the same incidence in this series as bilateral carotid occlusion.

In the vertebral arteries the sites of stenosis or occlusion were slightly more scattered than in the carotids but, like the internal carotid, the lesion was most common within 2 or 3 cm. of the origin of the artery (36 vessels). In the next part, extending from the sixth to the second cervical vertebræ, 17 vessels were affected; in the tortuous segment 8 arteries were stenosed or occluded; 4 vessels showed significant narrowing in the intracranial parts.

Thrombosis, which was found in 6 vertebral arteries (compared with 15 internal carotid arteries), was not significantly predominant at any point along the course of the vessels.

There was another type of lesion often responsible for narrowing of the lumen; this was the elevation of a plaque of atheroma by hæmorrhage into its depths (Fig. 2). Some of these lesions were recent and probably in part responsible for the terminal illness; others were older. Such lesions have been suggested as the frequent cause of coronary arterial occlusion and myocardial infarction (Paterson, 1936).

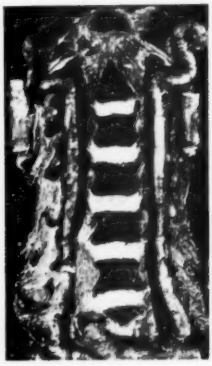


FIG. 1.



FIG. 2.

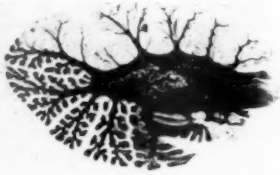


FIG. 3.

FIG. 1.—Dissected specimen showing the normal course of the proximal part of the vertebral arteries; the internal carotid arteries have been pinned to the side for display purposes.

FIG. 2.—Vertebral artery showing partial dissection of the arterial wall by a hæmatoma which had arisen in the depths of an atheromatous plaque. The lumen of the vessel is narrowed.

FIG. 3.—Complete loss of the granular cell layer in that part of the cerebellar cortex supplied by the superior cerebellar artery.

Sudden hæmatomata of this kind might indeed be responsible for the more prolonged episodes of neurological disability which characterise the clinical picture of stenosis of the carotid and vertebral arteries. They do not occur sufficiently frequently to account for minor attacks lasting perhaps only a few minutes and recurring several times in the day.

There is another phenomenon which I think is important in its effects on the cervical parts of the vertebral arteries—cervical spondylosis. In this disease the bony outgrowths that occur around the intervertebral joints may cause an anterior and lateral shift of the vessel. When the vertebral artery is otherwise normal, this change of course may be of little significance. If, however, it is already narrowed by atheroma, then movement of the neck, by enhancing the distortion, may cause complete blockage of the artery.

I will now consider the effects on the brain of stenosis of the vertebral arteries—at any rate those ischæmic effects that are indisputably obvious—cerebral infarcts. Out of the 100 cases only 35 showed actual infarction but in these 35 cases there were 74 distinct infarcts of which 16 were in the cerebellum, 4 in the brain stem and 5 in the territory of the posterior cerebral arteries. Of these 74 infarcts in the whole brain only 22 could be accounted for by occlusion or even stenosis of an appropriate local artery. This is even more striking when we consider the cerebellar infarcts since only one was of purely local origin, being an example of that relatively rare phenomenon, thrombosis of the posterior inferior cerebellar artery.

Most of the infarcts of cerebellum and brain stem resulted from failure of the hind-brain circulation either alone or, more commonly, as total cerebro-vascular failure resulting from carotico-vertebral stenosis (Hutchinson and Yates, 1957). There were only 7 cases in which the vertebral arteries alone were narrowed, the internal carotids being normal, and in only 2 of these did infarction result directly from this fact. One of these cases was the man of 47 referred to in an earlier paper (Hutchinson and Yates, 1957), who presented a final clinical picture not unlike thrombosis of the basilar artery. The remarkable thing about this case is that despite the many infarcts no local intracranial arteries were diseased and the carotids were normal. The cause of the five areas of infarction (bilateral and symmetrical in the occipital lobes, bilateral and symmetrical in the territory of the superior cerebellar artery and in the reticular tissue of the pons) was not discovered until the neck had been dissected. There was thrombosis of a large vertebral artery in its cervical portion, the other smaller artery being narrowed.

This symmetry in the pattern of infarction is, no doubt, a reflection of the unique arterial union which the vertebral arteries make to form the common basilar trunk. 8 of the cerebellar infarcts occurred as bilateral symmetrical lesions in 4 cases, either in the territory of the superior cerebellar arteries or at the junction of this territory with that of the posterior inferior cerebellar artery.

The phenomenon of infarction at the junctional zones is of some theoretical interest. These are the regions which are well supplied with anastomotic channels and are therefore

well protected from the effects of occlusion of any one local cerebral artery. However, when proximal stenosis of vertebral or carotid arteries reduces the flow of blood to both sides of the junctional zones simultaneously, then infarction will be most likely to occur in these areas. Such infarcts are characteristic of carotico-vertebral stenosis. It must be remembered that stenosis of the artery on one side of what would normally be a junctional zone causes the zone to shift in the direction of the poor blood supply. Thus the meeting of vertebral and carotid streams which normally takes place in the temporo-parietal and occipito-parietal regions may be unbalanced if there is proximal vertebral stenosis; the junctional point may then be the posterior edge of the cerebellum, the superior cerebellar arteries having become the extremities of the carotid circulation. Such derangements of the normal pattern of cerebral blood flow must be borne in mind whenever an explanation is sought for focal cerebral ischæmia and infarction.

Knowledge of the state of the proximal parts of the vertebral arteries throws considerable light on the ætiology of some forms of cerebellar degeneration. In particular the circumscribed foci of atrophy of cerebellar folia described by Lichtenstein and Levinson (1946) under the term "parenchymatous cortical cerebellar panatrophy" are clearly the result of ischæmia. Damage of this kind and even infarction of the cerebellum can occur when the local supplying artery is normal and patent, the diminution of blood supply being due to stenosis of the proximal or cervical part of the vertebral arteries.

There is another cerebellar lesion, the origin of which is in considerable doubt. Nevertheless, it seems to me that ischæmia due to proximal vertebral arterial occlusion has played at least some part in its production. The lesion is a selective degeneration of the granular layer of neurones from large areas of the cerebellar cortex. The remarkable feature of this degeneration is the complete preservation of the Purkinje cells and a layer of glial cells, forming a band between the pale granular layer and the molecular layer. I have not been able to demonstrate any marked glial or inflammatory cell reaction to this change.

The condition was present in 12 of the whole series of 100 cases; in some it was patchy and it was then most severe in the depths of the sulci at the extremity of the arterial blood supply; in others it involved almost the whole cerebellum. Occasionally the lesion was confined within the territory supplied by a single cerebellar artery. In one case this feature was strikingly obvious, the lesion being bilateral and symmetrical in the superior cerebellar arterial territory (Fig. 3).

I found that 8 of the 12 cases were diabetics and that this was about half the known diabetics in the whole series. However, several of the 8 were extremely mild diabetics and only 2 were in anything like diabetic coma before death. There were, moreover, 4 cases in which there had never been any evidence of diabetes. There was one factor that all 12 cases had in common and that was stenosis or occlusion of the vertebral arteries—indeed most had carotid and vertebral stenosis. 7 of the 12 had suffered infarction of the brain though this was not always of the cerebellum.

Selective granular degeneration has been reported before in adults. In 1943 Winkelman described 2 cases, the one an elderly diabetic the other a case of morphia poisoning with prolonged cyanosis. Bertrand and Godet-Guillain (1942) reported the lesion in 2 diabetics and 12 patients dying from carcinoma. However, in 1951 Brain *et al.* were unable to confirm this association with carcinoma and dismissed the lesion as being the result of post-mortem autolysis. The distribution and selective nature of the lesion makes this explanation unlikely.

In 1954 Hunter and Russell reported selective granular layer degeneration in a man of 37 who, 15 years previously, had shown cerebellar damage apparently the result of exposure to organic mercurial salts. This man had died of myocardial fibrosis secondary to coronary stenosis. There were also in this case severe atrophic changes of the calcarine cortex. I think that this pattern of lesions strongly suggests that failure of the hind-brain circulation might have been at any rate partly responsible for the changes; perhaps the mercurial salts acted by producing prolonged vertebral arterial vasospasm. In considering the ætiology of any mysterious degeneration of cerebellum, brain stem or occipital lobes a vascular cause cannot be excluded until the state of the proximal or extra-cranial parts of the vertebral arteries is known.

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To be continued: **Mr. Richard Johnson: Angiomatous Malformations and X-ray Therapy.**

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Section of Ophthalmology

President—R. C. DAVENPORT, F.R.C.S.

[*June* 13, 1957]

DISCUSSION: TONOMETRY

Dr. J. Gloster:

Ocular Rigidity and Tonometry

A tonometric determination of intra-ocular pressure involves an alteration in the shape of the eye. The eyeball is almost spherical and therefore its volume is the greatest possible for a given surface area, and, since fluids are incompressible, any alteration in the shape of the eye necessitates an increase in its surface area. The coats of the eye must therefore be stretched when the tonometer is applied and consequently the intra-ocular pressure is elevated artifically. It is this elevated pressure, P_t, which is measured by the tonometer but, for clinical purposes, one usually wants to know the pressure, P_o, which existed in the eye before application of the tonometer. It is in terms of P_o pressures that the tonometer must be calibrated. One method of achieving this is to connect the eye, via a cannula and a tap, to a reservoir by means of which the intra-ocular pressure can be set at known levels; having adjusted the reservoir, the tap is closed to isolate the eye, the tonometer is applied and its reading is noted. This is known as "closed stopcock" calibration and is clearly a direct way of relating P_o to readings on the tonometric scale. Despite its apparent simplicity, it was soon recognized that this procedure did not give consistent results, the tonometric reading varying from eye to eye at the same intra-ocular pressure. In contrast to the variability of "closed stopcock" readings, it was found that the so-called "open stopcock" readings were much more consistent from eye to eye. In "open stopcock" calibration, the eye is cannulated as before but remains connected to the reservoir during the application of the tonometer; with this arrangement, the intra-ocular pressure does not increase when the tonometer is applied and, in this respect, the procedure differs from the "closed stopcock" method and from the normal usage of the instrument.

Owing to the inconsistencies of the "closed stopcock" results, Friedenwald (1954) used the "open stopcock" method as the basis of tonometric calibration. However, the "open stopcock" method only enables one to relate tonometric readings to P_t values and, in order to complete the calibration, a further step is necessary by which P_t values can be converted to P_o values. For this calculation, one needs to know how great would be the increase of intra-ocular pressure for a given amount of tonometric distortion of the eye, and it has been found that this increase in pressure is the same as would occur if the eye, instead of being distorted, were distended by the injection of a volume of fluid equal to the volume displaced by the tonometer.

The relationship between a change in intra-ocular pressure and a change in intra-ocular volume depends ultimately upon the extensibilities of the various components which constitute the coats of the eye. For the rabbit eye, it has been shown that, when isolated strips of sclera and cornea are stretched, the change in tension and the extension do not conform to a simple law (Gloster, Perkins and Pommier, 1957). This is one reason why we might expect the relationship between intra-ocular pressure and intra-ocular volume to be complex, especially in view of the heterogeneous structure of the coats of the eye. The solution of this problem was attempted by Friedenwald (1937), who introduced the coefficient of ocular rigidity, K, which is given by the formula:

$$K = \frac{\log P_2 - \log P_1}{\triangle V}$$

where P_1 is the initial intra-ocular pressure and P_2 is the intra-ocular pressure after the injection of a volume of fluid, $\triangle V$ μl., into the eye. This expression was derived from the assumption that the proportional rise in pressure would vary directly with the proportional increase in volume, and Friedenwald claimed that the experimental findings of previous workers were in good agreement with the relationship which he had suggested.

Applying this expression to the calculation required for tonometric calibration, we have :

$$K = \frac{\log P_t - \log P_o}{V_c}$$

where P_t is the intra-ocular pressure with the tonometer resting on the eye (the open stopcock" pressure), P_o is the intra-ocular pressure before application of the tonometer and V_c is the volume of fluid displaced by tonometric distortion. The latter can be determined experimentally and, in order to relate P_t to P_o, it is then only necessary to assume a value for K. It is obvious that the calibration, calculated in this way, is accurate only for eyes having coefficients of rigidity equal to that adopted in the calculation also, the calibration is accurate for an individual eye only if K remains constant over the full range of pressures measurable with the tonometer.

At the Institute of Ophthalmology, Mr. Perkins and I have developed three methods for determining the coefficient of rigidity in animal eyes and in dead human eyes (Perkins and Gloster, 1957; Gloster and Perkins, 1957). Two of these methods depended upon simple distension of the eye, while the third involved distortion by a Schiotz tonometer. The

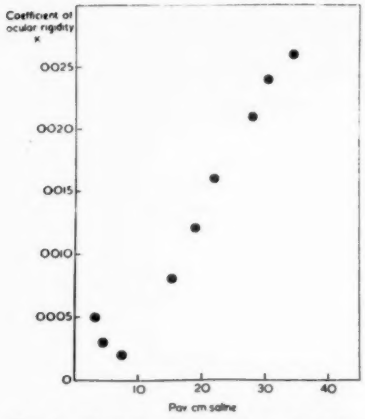


FIG. 1.—Variation of coefficient of rigidity with intra-ocular pressure. Enucleated rabbit eye. Manometric method. (P_{av} = mean of intra-ocular pressures before and after injection of fluid into the eye.)

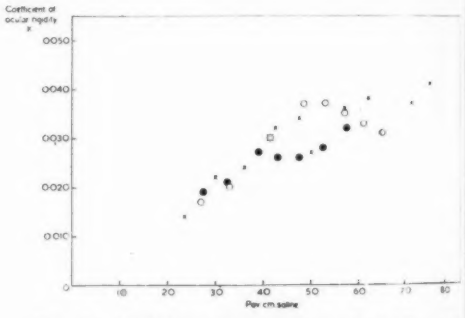


FIG. 2.—Variation of coefficient of rigidity with intra-ocular pressure. Enucleated rabbit eye. Tonometric method.

KEY: Black circle = weight of 5·5 grams on the tonometer
Cross = " " 7·5 " " " "
Open circle = " "10 " " " "

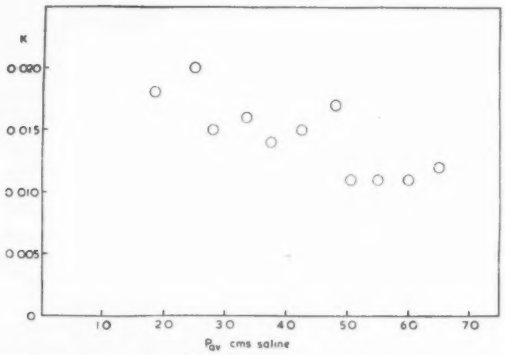


FIG. 3.—Variation of coefficient of rigidity, K, with intra-ocular pressure. Dead human eye in situ. Tonometric method.

results obtained by all three methods were in agreement. In particular, it should be emphasized that the coefficient of rigidity determined by simple distension of the eye was the same as that determined by tonometric distortion, a result which helps to clear up the doubt which has been apparent in the literature on this matter.

We found that in the rabbit eye the coefficient of ocular rigidity K was not a constant, its value increasing as the pressure at which it was measured increased (Figs. 1 and 2).

K varied in this way in both living and dead eyes, although its value was sometimes slightly greater in the latter. We also obtained some evidence which confirmed the observation by Ridley (1930) that the rigidity of the eye was increased after maintaining a high intra-ocular pressure for some time. Not only did the coefficient of rigidity vary with intra-ocular pressure in the individual eye but it also differed considerably from animal to animal, values from 0·007 to 0·031 being found at a pressure of 35 cm. saline in a series of ten rabbits. In all the rabbits the increase in K with increasing intra-ocular pressure was obvious, although this variation was more marked in some eyes than in others. In view of these findings, one would suppose that, even if consistent tonometric readings were obtained on a number of rabbit eyes by the "open stopcock" method, there would be discrepancies if the "closed stopcock" method were used and the correctness of this supposition has been demonstrated (Gloster and Perkins, 1957).

After developing the experimental techniques on the rabbit eye, Mr. Perkins and I applied them to the measurement of ocular rigidity in dead human eyes. Experiments have been done on eleven eyes (7 enucleated and 4 in situ) which were examined between eight hours and several days after death. Unfortunately, one does not know how closely results from these eyes indicate the rigidity of the living eye, although the values which we obtained for K did not differ greatly from those reported by other observers using tonometric methods on the living eye. As with the rabbit eye, there was no significant difference between the values of K determined by simple distension and those measured by tonometric distortion. We found that the coefficient of rigidity of the dead human eye varied with intra-ocular pressure but this variation was not as marked as in the rabbit eye. A more important difference from the rabbit eye was that, in all but one of the eleven human eyes, the values of K *decreased* as the intra-ocular pressure increased (Fig. 3); in the remaining eye there was a slight rise in K with increasing pressure. Mean values of K for the eleven eyes were 0·018 at an intra-ocular pressure of 25 cm. saline, and 0·013 at a pressure of 50 cm. saline. It is interesting that our finding that K decreases as the intra-ocular pressure rises in human eyes is in agreement with some observations of McBain (1957), although this author has not yet published details of his results. We found that K varied considerably from eye to eye, values from 0·012 to 0·027 being found at a pressure of 25 cm. saline, and values from 0·009 to 0·022 at 50 cm. saline.

The effect which a difference in the coefficient of ocular rigidity would have on tonometric calibration can be illustrated by the following example: Suppose two eyes, one having a coefficient of rigidity of 0·012 and the other a coefficient of 0·020, gave identical "open stopcock" readings on the scale of a Schiotz tonometer when the intra-ocular pressure with the tonometer resting on the eye (P_t) was 40 cm. saline. At this pressure, we have found that the volume of corneal indentation (V_c) produced by a Schiotz tonometer, using the 7·5 grams weight, was approximately 14 μl. Substituting these values for K, P_t and V_c in the equation given above, P_o is found to be 27·2 cm. saline for the eye in which K is 0·012, while P_o is 21·0 cm. saline for the eye in which K is 0·020. Thus, the same scale reading would be indicated by the tonometer although the initial pressures in the two eyes differed by about 6 cm. saline.

The calibration charts usually issued with the Schiotz tonometer have been calculated assuming a coefficient of rigidity of 0·0215, which was considered by Friedenwald (1954) to be the average value for the human eye. These charts are therefore perfectly accurate only for eyes having K equal to 0·0215. It has been suggested that errors due to variations in K may be overcome by taking readings with different weights on the tonometer—this, incidentally, might be considered an advantage of the "weighted" as compared with the "weightless" Schiotz tonometer. If readings with different weights indicate the same intra-ocular pressure, they may be considered reliable, since the eye examined must have the same coefficient of rigidity as that adopted for calculating the calibration. It has been claimed that tonometric readings taken with two different weights can be used to measure the coefficient of rigidity and that this allows one to make a correction for any departure from the assumed value of K; however, in our experience, even under ideal conditions this method may yield grossly inaccurate results (Gloster and Perkins, 1957).

Whilst is has been recognized that variations in ocular rigidity are partly responsible for the lack of consistency of "closed stopcock" readings, it is clear that this difficulty cannot be completely overcome by basing tonometric calibration on "open stopcock" readings and then applying a calculation which utilises an average value for the coefficient of rigidity. This is probably the best practical approach to the calibration of the Schiotz tonometer, provided that the inadequacies of the procedure and the limitations imposed thereby are not forgotten. From the purely theoretical aspect, it is evident that accurate calibration of a tonometer demands a minimal difference between P_t and P_o, and this can be achieved only by reducing the tonometric distortion of the eye, a matter which is entirely dependent upon the design and construction of the instrument.

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Mr. E. S. Perkins:

Dr. Gloster has outlined some of the theoretical problems involved in tonometry and I shall discuss some of the instruments in use to-day in the light of this theoretical background.

The ideal tonometer should produce no alteration in the intra-ocular pressure and be accurate for any eye and pressure; it is obvious that we are still far removed from such an ideal and must content ourselves with an instrument which produces as little change in shape of the eye as possible. It is only in this way that errors due to variations in ocular rigidity can be avoided. In essence this means a light weight only must be applied to the eye. In addition the instrument must have a low reading error, a good mechanical design and it must cause no injury to the eye. It should be relatively easy to use so that reliable readings can be obtained by junior staff. In addition it should be easy to sterilize, as infection can undoubtedly be transmitted from eye to eye by tonometers. These points are summarized in Table I.

TABLE I.—TONOMETER—DESIDERATA

1	Small distortion of globe
2	Light weight
3	Low reading error
4	Stable mechanical design
5	Non-traumatic
6	Easy to use
7	Easy to sterilize

The two main types of tonometer in use today depend either on indentation or applanation of the cornea. Each type may be further subdivided into (*a*) instruments in which a constant force (e.g. a weight) is applied to the eye and the resulting indentation or applanation measured, and (*b*) instruments in which the force required to produce a constant indentation or a constant area of applanation is measured.

Examples of instruments of these four types will now be discussed in relation to our ideal requirements.

The Schiotz tonometer is an indentation tonometer in which a constant force is applied and the resulting indentation measured. Now we have many criticisms to make of the Schiotz tonometer, but in all fairness to its inventor it must be accepted that in a large proportion of cases it will provide a useful indication of the state of the ocular tension, and it has undoubtedly been of major importance in the development of our clinical knowledge of glaucoma.

Our first ideal requirement was a small distortion of the globe, and immediately we find the Schiotz tonometer at fault. The distortion and consequent rise in intra-ocular pressure which follows application of the Schiotz tonometer to the eye are very considerable and not fully appreciated by most people using it.

Table II shows some results obtained on cadaver eyes in which a needle connected to a

TABLE II

P_o AND P_f VALUES ON FOUR HUMAN EYES, USING A SCHIOTZ TONOMETER WITH 7·5 G. WEIGHT

Cadaver eye	P_o cm/saline	P_f cm/saline	K
I	30	39	·013
II	30	48	·019
III	30	48·5	·021
IV	30	44·5	·014

reservoir was inserted into the anterior chamber so that the intra-ocular pressure could be maintained at a given pressure. A tap on the connexion between the needle and the reservoir was then closed and a Schiotz tonometer lowered on to the eye. By comparison with an

"open stopcock" calibration made on the same eye, the pressure in the eye while the tonometer was resting on it could be calculated. It will be seen that in all four eyes a very appreciable rise in pressure took place when the tonometer was placed on the eye. The figures for the scleral rigidity of each eye were also calculated for this pressure and it can be seen that the rise in pressure is roughly proportional to the rigidity.

Now it is P_t that the tonometer measures, and the true intra-ocular pressure can only be an assumption from this value. The calibration curve used in practice is compounded from experimental data on animal and human eyes and involves a theory of scleral rigidity which certainly does not hold true for rabbit eyes, and probably does not hold true for all human eyes.

Figs. 1 and 2 show the calibration curves of a Schiotz tonometer on rabbit eyes of differing

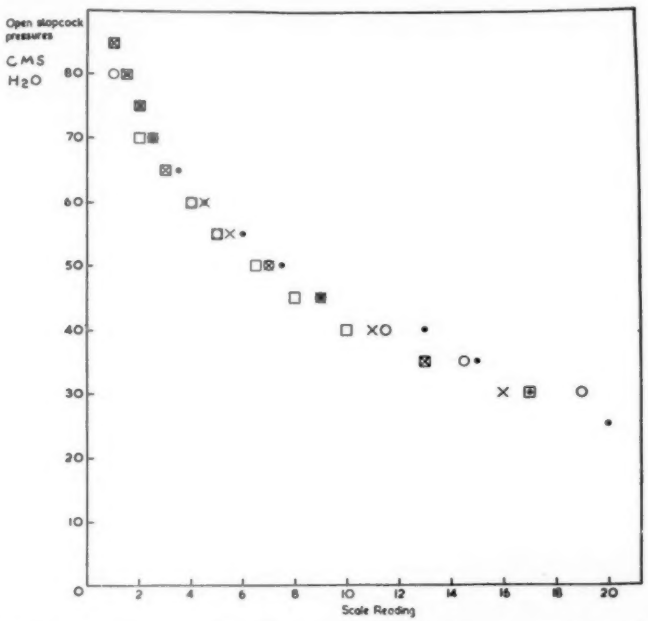


FIG. 1.—' Open stopcock" calibrations of a Schiotz tonometer on four rabbit eyes. The 4 different symbols indicate 4 different rabbits.

scleral rigidities. Fig. 1 shows the "open stopcock" calibration curves using the same tonometer on four eyes. The results are fairly consistent but in Fig. 2, which shows "closed stopcock" readings on two of the eyes, it is clear that the same scale reading on the tonometer corresponded to widely different intra-ocular pressures in the two eyes.

As with most types of tonometers, variations in corneal curvature and thickness introduce errors into the reading of a Schiotz tonometer. These have been fully investigated by Friedenwald (1954) and it is possible to correct for these errors, though it is hardly a practical proposition for clinical use.

The Schiotz tonometer is not free from the danger of trauma to the eye, and while being fairly easy to use, it not so easy to sterilize.

The Mueller electronic tonometer works on exactly the same principle as the Schiotz and is open to the same objections with regard to the degree of distortion of the globe it produces.

The principle of measuring the force required to produce a standard indentation of the cornea has not been much exploited up to now, but Maurice, at the Institute of Ophthalmology (1957) has two instruments of this type under development and trial at the moment. As the depth of indentation can be made small, the resulting distortion is much less than that of the Schiotz tonometer and, therefore, should produce a much smaller rise in pressure when applied to the eye. One of these instruments has been designed to give continuous

recording over prolonged periods, and should prove a most useful research tool. The other is designed for clinical use.

Maklakoff (1885) appears to have been the first person to appreciate the possibilities of applanation tonometry, and he solved the problem of measuring the area of applanation produced by a flat-ended weight of 5 grams by putting Bismarck brown on the cornea first

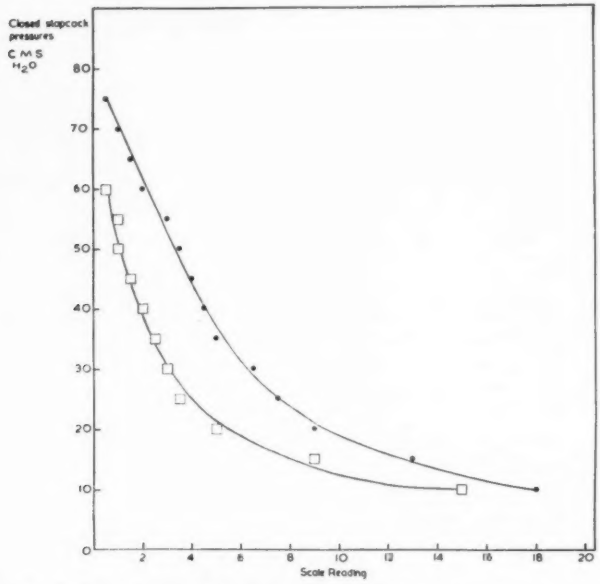


FIG. 2.—"Closed stopcock" calibrations of a Schiotz tonometer on two rabbit eyes. The 2 symbols represent the same 2 rabbits as in Fig. 1.



FIG. 3.—The applanation tonometer and brass ring.

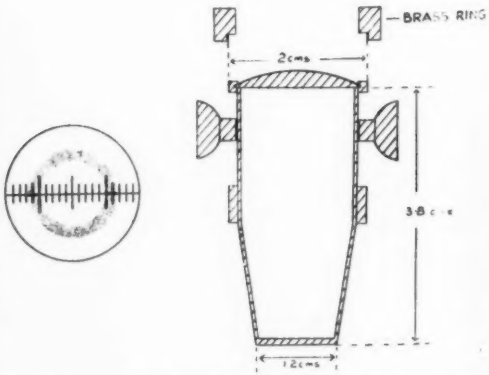


FIG. 4.—Diagram of the apparatus and a view of the scale as it appears in use. The shaded ring represents the circle of fluorescein.

and then printing the area of contact on to filter paper. This method is obviously open to serious errors and better methods are available. In 1953, I produced a simple applanation tonometer, primarily for use on laboratory animals some years ago. It consisted of a small perspex cylinder with a flat surface at one end and a viewing lens at the other (Figs. 3 and 4).

Circles or a scale were engraved on the flat end at ½ mm. intervals. A drop of 0·2% fluorescein was put on the cornea and the instrument rested on the cornea. The diameter of the applanation surface was compared with the engraved scale. The diameter can be read to within ½ mm. with this instrument and while this degree of accuracy is adequate at low intra-ocular pressures, the reading error increases badly at high pressures, as shown from the calibration curve in Fig. 5. We are working on another model in which an optical

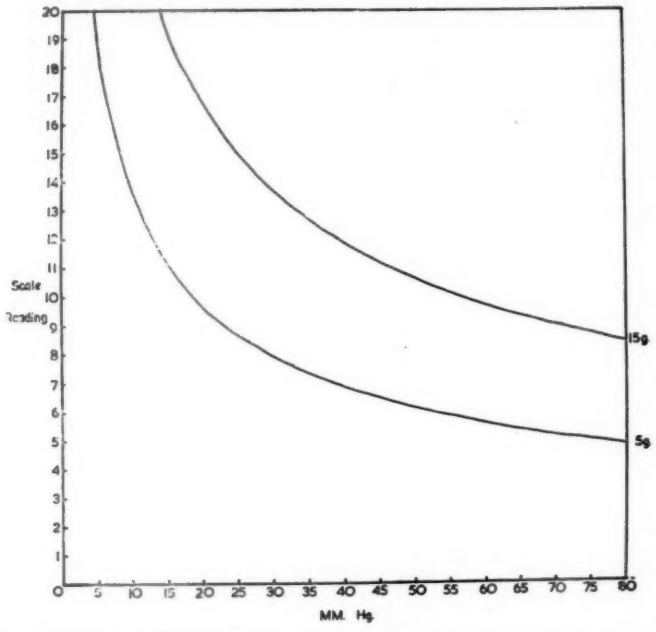


FIG. 5.—Theoretical calibration curves for the tonometer alone (5 grams) and with the extra weight (15 grams).

Figs. 3, 4 and 5 are reproduced by permission of the Editors, *Trans. ophthal. Soc. U.K.*, (1953), **73**, 261.

doubling system is used, and with this readings of the diameter of applanation can be made to 0·1 mm.

These types of tonometer have the advantage that they are light in weight and cause very little distortion of the cornea, so that errors due to scleral rigidity are minimized. The reading error can be made quite small and the instruments are mechanically simple and robust. They are, however, more difficult to use than the Schiotz type of tonometer, but can be easily sterilized and are non-traumatic.

Goldmann (1954) has recently designed an ingenious applanation tonometer used with the Haag-Streit slit-lamp which measures the force required to produce a constant area of application. By keeping the area of applanation constant the force in grams is proportional to the theoretical intra-ocular pressure from the formula:

$$P = \frac{W}{SA}$$

where P = intra-ocular pressure in mm.Hg
W = weight applied
S = specific gravity of mercury
A = area of applanation

This is the general theoretical formula for applanation tonometry. Now if this formula is correct it should be applicable to any eye. Goldmann has so far published no experimental work to justify the application of this theory, but some experiments of Dr. Gloster and myself suggest that it is not universally correct and that certain other factors are concerned.

While it would appear, therefore, that applanation tonometry offers some advantages over the usual indentation methods, more work must be done before the theoretical calibration can be accepted.

A small pressure-sensitive capsule has recently been developed which can transmit a radio signal from which the pressure of its surroundings can be determined. Perhaps in the future we shall simply implant such a transducer into the eyes of our glaucoma patients and tune in to obtain their intra-ocular pressure without touching the eye; until that time, however, we must endeavour to improve our present methods and always bear in mind the many errors and inaccuracies involved.

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Dr. C. R. S. Jackson:

Standardization of X-Tonometers

We know now, and Friedenwald (1937) must be given credit for stimulating interest in this aspect of the problem, that the intra-ocular pressure is only one of a number of factors which influence the performance of an instrument of the Schiotz type. This interest is, however, of fairly recent development and I imagine that one of our duties is to restrain a tendency among our colleagues to believe too slavishly in what our tonometers tell us. I should like to persuade people to get away from the tendency to read tonometers to half-millimetres of mercury, though I admit that the present calibration charts imply a degree of accuracy of this order.

Another thing we sometimes fail to remember is the wide scatter of normal readings. Both Friedenwald (1937) and Jackson (1955), with others, have drawn attention to this previously, and Fig. 1 shows the distribution of the scale readings in a new series of 405 normal eyes, using an American standardized tonometer with a 5·5 grams load. Although the readings are distributed fairly symmetrically about the mean reading of 4·5 scale divisions (which gives a reading for the intra-ocular pressure of something just under 20 mm.Hg), the actual range of apparently normal values is considerable. I shall discuss my results purely in terms of scale divisions: I am not particularly concerned with the interpretation of my readings, but rather with the effort to obtain comparable readings from different tonometers.

The work of the American Committee on Standardization of Tonometers, the subsequent adoption of the standard for the original Schiotz tonometer by the International Committee, and the move of the Ross Foundation in following the American lead, and of the Faculty of Ophthalmologists in supporting this move, are all now well known.

All the foregoing work has been confined to the original model of Schiotz's tonometer, the one with weights. This is the most popular tonometer in the United States, but here, and in Scandinavia, there is a considerable demand for the X-tonometer, with no weights to take off and lose, and with its convex-ended plunger. Through no fault of their own, the manufacturers have not been able to make these tonometers to any uniform pattern, owing to lack of guidance from the profession, and divergent results have been obtained from instruments supposedly similar. Also, we have been faced with the difficulty of relating the readings of such X-tonometers to those obtained with the standardized weighted instruments. An attempt has therefore been made to find a way of overcoming these problems.

It was first necessary to decide what yardstick of construction we were to use and this has been done after an examination of Schiotz's original descriptions of his tonometer without weights. The basic design of the two instruments, weighted and weightless, is similar, and it has been quite easy to draw up a specification for our proposed standard X-tonometer. Table I shows the ways in which the two instruments differ in their

TABLE I.—SPECIFICATION

	Schiotz	X-tonometer
Weight of plunger assembly	5·5 g.	5·2 g.
Tonometer without handle	16·5 g.	16·2 g.
Plunger diameter	3 mm.	3 mm.
Plunger tip	Concave radius 15 mm.	Convex hemispherical radius 1·5 mm.

The zero for the X-tonometer to be set when plunger tip is 0·05 mm. below footplate.

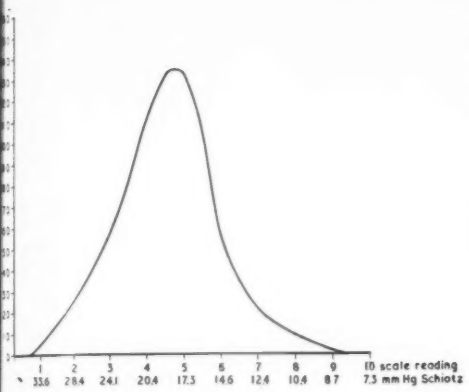


FIG. 1.

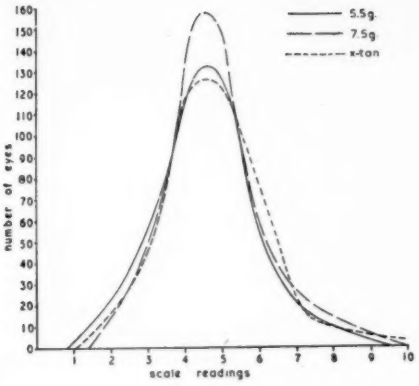


FIG. 3.

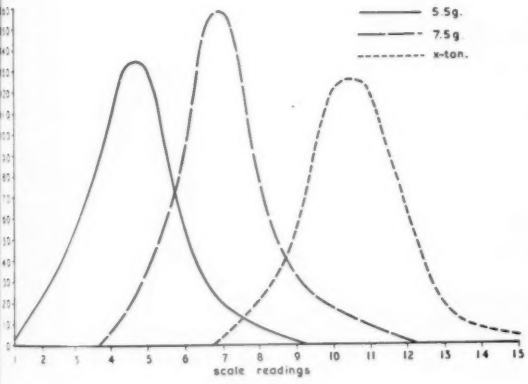


FIG. 2.

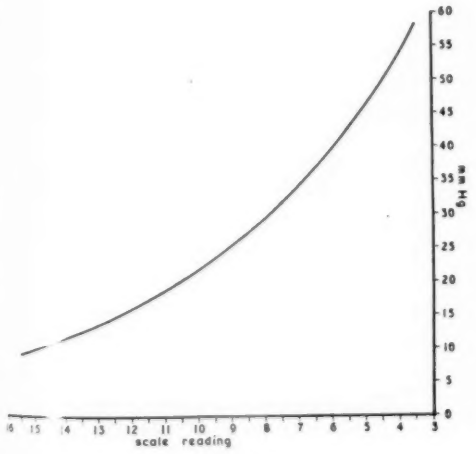


FIG. 4.

specifications. In all other respects the X-tonometer is the same as the original model. There seem to be advantages, from the manufacturing point of view, in keeping the basic design of the two instruments similar.

A useful confirmation of the reasonableness of my ideas for the X-tonometer has come from Copenhagen, where Dr. Mahneke (1957) has arrived at identical figures in his consideration of what the X-tonometer should be like. A prototype has been constructed to this specification and I hope to persuade the instrument makers to build their X-tonometers to this pattern. Even if further experience suggests that a change is necessary, no harm will have been done.

Having then obtained a prototype X-tonometer, it had to be calibrated, and I decided to do this on living eyes, as the use of cannulated excised eyes seemed to introduce a number of difficulties. The instrument used for comparison was a standardized weighted tonometer made by Meyrowitz and recently checked with regard to its compliance with the accepted specification.

Three readings were made on each eye; with the Schiotz 5·5 grams and 7·5 grams loads, and with the X-tonometer. The order in which the instruments were applied was varied

in a random way and the tonometer rested on the eye only long enough for a steady reading to be obtained. It has, I think, been shown that a brief application of a tonometer does not significantly alter the subsequent readings.

The number of eyes used was 601, of which 405 were normal and 196 pathological. The pathological eyes were mostly from our glaucoma patients, while the normal eyes were all eyes in which no suggestion of ocular disease had been raised. They were eyes which had been anæsthetized for the purpose of treating some extra-ocular condition, syringing of tear passages, incision of a cyst, and so on. It is with these normal eyes that I am now mainly concerned.

I first sought to establish that two instruments with differently shaped plungers behave in a comparable way on a series of eyes, for it has been suggested that the shape of the plunger-end governs the character of the corneal indentation. If, therefore, the X-tonometer was behaving in a manner unrelated to that of the standard tonometer, one would expect the shape of the distribution of the readings to vary as between the instruments. Fig. 2 is a graph showing the number of eyes at each reading. There is a maximum occurring at about the centre of the range in each case, while the readings are approximately evenly distributed on each side of this.

We were next looking for a way of relating these readings to one another, and, after attempting a number of mathematical treatments, it transpired that the most useful manœuvre was to correct each reading by a factor based on the differences of the means. The mean of the readings on 405 normal eyes lay at 4·5 scale divisions for the 5·5 grams load, at 7·1 scale divisions for the 7·5 grams load, and at 10·6 scale divisions for the X-tonometer. If each reading is moved toward the 5·5 grams curve by the appropriate correction factor, the superimposed curves appear as in Fig. 3.

The all-over pattern is satisfactory, but it remains to show how closely the individual corrected readings correspond.

I have applied the correction factors to each reading in this series, in both the normal and pathological eyes, and have expressed the results in a rather crude way, but one which seems to show what we want. The results are expressed in terms of the percentages of the corrected readings which lie within a given distance of the chosen standard (Table II).

TABLE II.—THE EFFECT OF CORRECTION FACTORS

	Normal %	Normal %	Path. %
	Related to 5·5 g. Schiotz		
Corrected 7·5 g.	± 0·5	83·9	82·1
	± 1·5	99·2	96·6
Corrected X-ton.	± 0	40·9	49·6
	± 1	89·3	89·5
	Related to 7·5 g. Schiotz		
		Normal %	Path. %
Corrected X-ton.	± 0·5	73	74·9
	± 1·5	95	94·5

Whether these divergences from theoretical accuracy are due to mechanical faults, to reading difficulties, or to the influence of factors other than the intra-ocular pressure I do not know, but at least this simple technique, which brings about 90% of our readings to lie within ±1 scale division of each other is sufficiently good for the present state of accuracy of our instruments.

There is something to be said for recording the results of our tonometry simply in terms of scale readings and of the weight used, but it will be difficult to get away from the practice of converting these readings into millimetres of mercury. Fig. 4 shows the currently accepted conversion chart for the Schiotz tonometer, modified to fit in with the specification outlined for the X-tonometer.

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Section of Odontology

President—J. A. S. WRIGHT, A.F.C., F.D.S. R.C.S.Eng., H.D.D., F.D.S. R.C.S.Ed.

[*February* 25, 1957]

An Examination of Dentine for A and B Blood-group Antigens by the Mixed Agglutination Technique

By IVOR R. H. KRAMER, M.D.S.Lond., L.D.S.Eng.

Department of Pathology, Institute of Dental Surgery
(British Postgraduate Medical Federation)

BY a recently developed technique (Coombs and Bedford, 1955) blood-group antigens have been demonstrated in blood platelets, in adult epidermal cells (Coombs *et al.*, 1956), and in fœtal epidermal cells (Fuchs *et al.*, 1956). The presence of these substances in cells other than erythrocytes may have applications to problems in fields as varied as tissue grafting, the determination of fœtal blood group, and in forensic medicine. Therefore, it was thought to be of interest to apply the method to a calcified tissue; dentine was chosen as it has a higher ratio of cell substance to matrix than bone, and is easier to obtain free from blood.

Principle.—The method devised by Coombs and Bedford overcame the difficulty of performing direct agglutination experiments on tissue cells which do not form suitable agglutinable suspensions. The cells under investigation were exposed to sera containing the blood-group agglutinins anti-A and anti-B, and then washed free of excess serum. When re-suspended, these treated cells were mixed with washed erythrocytes of known blood group. It was found that, when the cells under test came from an individual of group A, exposure to serum containing anti-A resulted in a linking of anti-A to the cells, so that when subsequently mixed with group A erythrocytes, these erythrocytes adhered to the surfaces of the test cells. Corresponding results were obtained with cells from individuals of group B, whilst cells from group AB individuals could be "sensitized" by both anti-A and anti-B sera so that subsequently both group A and group B erythrocytes would adhere to them.

Present method.—Carious and non-carious teeth extracted under nitrous oxide anæsthesia were collected immediately after extraction, and a sample of capillary blood was obtained from each patient whilst under the anæsthetic. The blood samples were used for determining each patient's ABO blood group.

Dentine powder was prepared from each newly-extracted tooth by the following method: After preliminary washing to remove blood and debris, the tooth roots were ground on a carborundum wheel to remove the cementum. The roots were then severed from the crown, split open, and the pulp and pre-dentine removed by scraping and dental burs. The root dentine thus obtained, and freed as far as possible from pulp and cementum, was powdered in a steel mortar and passed through a 300-mesh sieve. Thus, a series of samples of powdered dentine were obtained, each sample derived from a tooth or teeth of an individual of known ABO blood group.

A small portion of each sample was then exposed for one hour at approximately 20° C. to undiluted anti-A blood grouping serum (from the Blood Group Reference Laboratory, Lister Institute) and another portion was similarly exposed to anti-B grouping serum. Following exposure to these sera, the dentine powder was centrifuged and washed three times with a large volume of Ringer's solution, and the washed powders were mixed with 2% washed erythrocyte suspensions as follows:

Dentine powder treated with			Erythrocytes
Anti-A serum		+	A
A	,,	+	O
B	,,	+	B
B	,,	+	O

The dentine powder-erythrocyte mixtures were centrifuged, the deposit was loosened by gently tapping the tube, and a portion of the sediment was withdrawn with a fine pipette, placed on a slide under a coverslip, and examined under the microscope. No evidence of erythrocyte adherence to the dentine particles was found in any preparation.

It was thought that the negative findings might be the result of inaccessibility of blood-group substances in the dentine because of the high degree of calcification. Therefore, the experiments were repeated on dentine powder decalcified by exposure for ten minutes to N/10 HCl. However, again no dentine powder-erythrocyte agglutination could be detected.

Conclusions.—Using a simple modification of the mixed agglutination technique for the demonstration of A and B blood group antigens in human epidermal cells, it has not been found possible to demonstrate these substances in human dentine.

Acknowledgments.—I am indebted to Mr. W. G. Armstrong, M.Sc., and Mrs. V. Gilchrist for preparing the dentine powder, and to Mrs. V. Markies for technical assistance.

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[*March* 25, 1957]

Cervico-facial Actinomycosis with Acute Presentation.—H. P. COOK, M.B., B.S., B.D.S., F.D.S. (for B. St. J. Steadman, L.R.C.P., M.R.C.S., B.D.S.).

Male, aged 16. One week's history of difficulty in opening his mouth, followed four days later by intra-oral swelling related to $\overline{8}|$, and marked external swelling at the angle of the mandible.

He was treated with four-hourly hot mouth washes and intramuscular penicillin, but failed to respond and was admitted. Temperature rose to 103·5° F. and intra-oral incision was carried out. Pus grew normal mouth flora. Temperature was normal for twelve hours, then rose to 103° F.

External incision and drainage carried out. Pus—smear: Gram-positive branching filaments. Culture: *Actinomyces israeli.*

Therapy.—Penicillin crystalline 4,000,000 units i.m. b.d. for thirty-two days. Streptomycin ½ gram b.d. i.m. for five days, from the seventh and the twenty-second days.

All signs and symptoms disappeared on this therapy. No relapse after six months.

Probable portal of entry of organism: erupting wisdom tooth crypt.

Fracture of Mandible.—JOHN CAMBROOK, M.R.C.S., L.R.C.P., F.D.S.

A. W., aged 35. He received a blow on his right mandible from the skull of an opponent during a game of football.

He was seen four days later when X-rays showed a vertical fracture through the socket of a horizontally impacted $\overline{8}|$.

There was a very slight vertical deformity of the posterior fragment. Penicillin therapy was started, $\underline{8}|$ extracted and splints cemented on the following day.

After twenty-four hours the fracture was reduced and the splints immobilized. Penicillin was discontinued after seventeen days.

The interest of the case, which was shown five weeks after the injury, was the method of causation and the extremely good state of the mouth due to the hygiene practised by the patient; also the manner in which he had been able to take food, maintaining both his weight and sufficient energy to carry on with his training.

Erosive Lichen Planus of the Mouth.—JOHN CAMBROOK, M.R.C.S., L.R.C.P., F.D.S.

C. H., aged 68. He had an operation for leucoplakia of the anal region—June 1956. During convalescence he noticed slight skin rash on his left arm and right leg.

Four months later he complained of soreness of the inside of his cheeks. His dentures were adjusted but without relief. Treatment with local penicillin and Bradosol produced no improvement. He was consequently referred to me when he had a large area of superficial ulceration inside the cheeks extending on to the gums. The appearance was similar to aspirin burns and there were no lines or striations of lichen planus. Bacteriology showed no significant organisms or fungi.

The lesions on the limbs were confirmed as lichen planus by Dr. Lipman Cohen.

Shortly afterwards the usual characteristics of lichen planus were seen in the mouth and on the lips. It was felt that initially the mouth had been overtreated, so that only a local application of 10% silver nitrate to the raw areas was made twice weekly, and the condition had markedly improved.

Chondrosarcoma of the Maxilla and Septum.—GEORGE T. HANKEY, O.B.E., T.D., F.D.S., M.R.C.S.

B. T., female, married, aged 54.

1.2.56: First noticed a painless infra-nasal swelling, which made her nose look crooked. A month later she removed two upper incisors because they had become very loose: later still |3 was extracted by a dental surgeon for acute infection. For a while the swelling decreased, then got steadily larger. Referred by her doctor to St. Bartholomew's Hospital on 26.5.56.

On examination.—The upper lip was pushed out and the floor of the nose and left ala nasæ were raised by a swelling which was expanding the whole pre-maxillary alveolus. The swelling was tense and the mucous membrane over it slightly reddened. 21|123 had been recently extracted, but there was still a sinus of the |2 socket up which a probe could be passed 2 to 3 cm. upwards and backwards with the sensation of contacting soft tissue: no bone felt. X-rays (Fig. 1) suggested a large dental cyst in the mid-line occupying a position between the hard palate and the floor of the nose.

Operation (15.6.56) (four and a half months after swelling was first noticed).—Buccal approach: reflection of an infra-nasal mucosal flap exposed a firm encapsulated tumour: consistency soft and friable, calcified in places, colour pinkish grey. Removed by blunt dissection, leaving a space 4 × 4 × 3 cm. between the roof of the hard palate and the remainder of the nasal septum. Part of the epithelial lining of the floor of the nose unavoidably removed with the growth. Buccal approach closed with sutures and the cavity packed via the nose with B.I.P. on gauze. Uneventful convalescence.

Histopathology.—Posterior nasal specimen: Greyish tissue with well-circumscribed capsule. Mottled grey, fawn and brown appearance on cut surface. Well-differentiated cartilaginous masses in some areas and, in others, necrosis of cartilage, the latter occupying most of the section (Fig. 2). Some evidence of ossification of cartilage in one or two areas. Many areas of myxomatous degeneration.

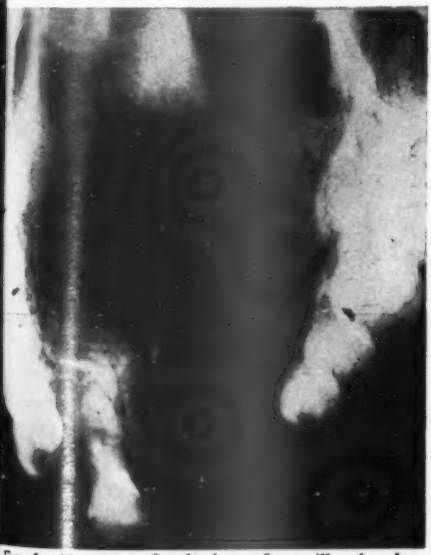


FIG. 1.—X-ray—occlusal view of maxilla showing outline of tumour, with centre structureless and rarefied as in cyst.

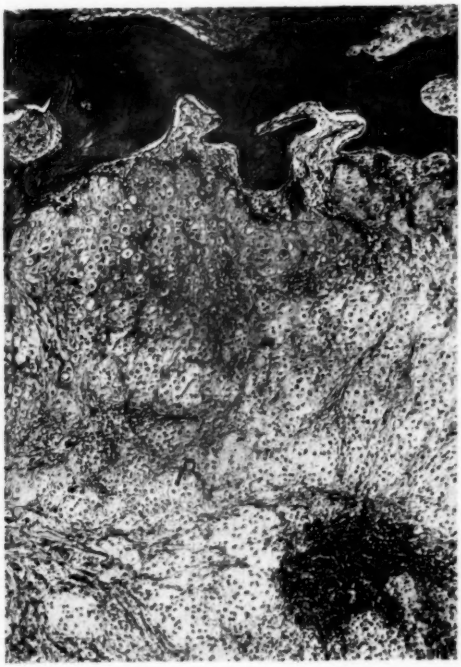


FIG. 2.—A fairly well-differentiated cartilaginous area, → but some irregularity of cells and hæmorrhage present. Stained H. and E. × 39.

Anterior oral specimen: Sections show a rather different picture. The cartilaginous material is somewhat irregular in its arrangement, but still well differentiated, the nodules being separated by a rather loose cellular fibrous tissue in which the new formation of cartilage can be seen. There are areas of ossification and calcification and frequent hæmorrhages and necroses. While the appearances are generally those of a well-differentiated chondroma, the irregularity and the rather young connective tissue component suggest that there may be a low-grade malignancy in the tumour.

Comment.—Miles (1950) summarizes the literature and behaviour of six previously reported cases and adds two more himself. Their degree of malignancy varies; they are not sensitive to radium or deep X-rays; radical surgery would seem to have the best prognosis.

To date the patient is well, with no sign of recurrence.

Acknowledgments are due to Dr. R. J. R. Cureton for the histopathology and photomicrographs and to Mr. R. F. McNab Jones for the after-care of the nose.

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Primary Squamous-cell Carcinoma of Mandible arising from Epithelial Lining of Dental Cyst.—GEORGE T. HANKEY, O.B.E., T.D., F.D.S., L.R.C.P., M.R.C.S., and J. A. PEDLER, M.D.S., F.D.S., L.R.C.P., M.R.C.S.

History and treatment (*G. T. H.*).—Man, aged 75, retired carpenter.

History of one month's painless enlargement of left side of mandible. 14.1.57: First attended dental department of The London Hospital with a tense reddened swelling below the left border of mandible. First impression was a cellulitis resulting from many septic teeth. Radiographs (Fig. 1) showed cystic area extending from $\overline{3}$ to $\overline{8}$ region. A few days later the swelling was more tense and external incision resulted in evacuation of a pus-like material. *Bacteriological culture* showed saprophytic growth only; no pyogenic organisms. The swelling did not subside and a slight discharge continued. No intra-oral sinus or communication with cyst. Pre-operative dental extractions were begun.



FIG. 1.—Radiograph of left body of mandible—occlusal view.

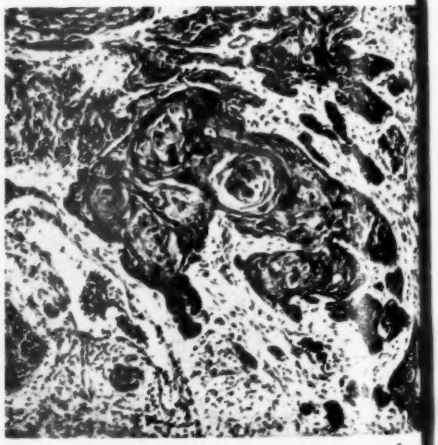


FIG. 2.—Keratinizing squamous cell carcinoma from tissue adjacent to mandible. × 8.

22.2.57: *Operation under general anæsthesia.* External approach by incision beneath lower border of mandible. After evacuation of about 1 oz. of thin, cheesy material the swelling was found to consist of soft, pink, friable tumour-like tissue with no encapsulation. The lesional tissue was invading the soft tissues of the neck and was emerging from an erosion in the lower border of the mandible. The lesional tissue was removed as widely as possible and the cavity in the mandible was cleared. There was no opening into the mouth.

Histopathology (*J. A. P.*).—Material from three sites was received for examination.

(1) From lesion external but adjacent to mandible; four irregular rubbery grey-brown fragments. Microscopically this consisted of a mass of keratinizing squamous cell carcinoma (Fig. 2).

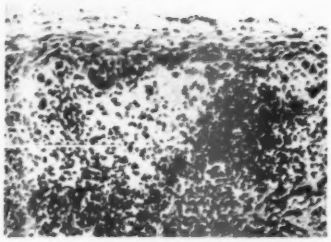


FIG. 3.—Typical dental cyst lining from cavity of mandible. A, squamous epithelium. B, fibrous wall with chronic inflammatory infiltration. × 73.

(2) From tissue lining the cystic cavity within the bone of the mandible; two rubbery grey-brown sheets (the larger 1·8 × 0·8 × up to 0·2 cm. thick). Microscopically the appearance varied from place to place but extensive areas were consistent with a typical dental cyst, i.e. a fibrous cyst wall with heavy infiltration of chronic inflammatory cells and a lining of stratified squamous epithelium (Fig. 3). Some parts of this material showed evidence of malignant change.

(3) From orifice of sinus in cervical skin; fragment of skin 1·5 × 1·1 × up to 0·5 cm. thick with a ragged through and through aperture. Microscopically this consisted of a keratinizing squamous-cell carcinoma comparable with the material originating just adjacent to the mandible.

Conclusion.—The presence of extensive dental cyst-lining with some areas of early malignant change, associated with a frank squamous carcinoma eroding the mandibular cortex and invading the tissues of the neck to become attached to skin, is regarded as good evidence that this is a case of primary carcinoma arising in a dental cyst lining.

8.3.57: *Post-operatively* a course of X-ray therapy was instituted.

[*April* 29, 1957]

Acute Monocytic Leukæmia.—H. P. COOK, M.B., B.S., B.D.S., F.D.S. R.C.S.

Acute monocytic leukæmia is one of the uncommon types of leukæmia. There are only 13 cases recorded at the Westminster Hospital in the last ten years. This case terminated fatally after a very rapid course, the total duration of symptoms being only three and a half weeks.

Patients with this disease often present as a dental problem. Fitzgerald (1943) reported a case in which the swollen gums were initially treated as Vincent's infection. The gingivæ are, in fact, very constantly affected. In a review of 133 cases of monocytic leukæmia, Osgood (1937) found that in the 88 cases in which the gums were mentioned, 80% showed swelling and ulceration.

Case history.—Female, aged 48. Her gums had become swollen and painful during the previous two weeks. Over the same period, she had suffered intermittent headaches, felt tired and weak, and became breathless on exertion. After a week of these symptoms, she saw her doctor and dentist in consultation. They prescribed intramuscular penicillin and oral vitamin B, which were given for eight days without benefit.



FIG. 1.—Marked gingival enlargement.

Examination.—The patient looked ill, her features were pale and muddy and she had an air of great lassitude. Temperature 99° F.

The gingivæ showed marked generalized swelling, most obvious anteriorly in relation to some bridge work (Fig. 1). The enlarged tissue was purplish in colour and partially covered the tooth crowns on buccal and lingual aspects. No spontaneous hæmorrhage or ulceration was seen at this stage.

She was not clinically anæmic. There were enlarged, soft, discrete, mobile lymph nodes bilaterally palpable in the axillary, inguinal, cervical and supra-clavicular groups. The spleen was palpable (two fingers) and the liver edge just felt.

Investigations.—Hess test negative.

Chest X-ray normal.

Full blood count: Hb 85%; R.B.C. 3,900,000/c.mm.; W.B.C. 90,000/c.mm. (polymorphonuclear neutros 5%, eosinophils 1%, lymphocytes 4%, monocytes 86%, monoblasts 2%, myelocytes 1%).

Sternal marrow: Total nucleated count—400,000/c.mm. A sheet of abnormal monocyte-like cells in all stages of development, with reasonable numbers of myelocytes and nucleated red cells.

She was put on Prednisone 10 mg. t.d.s. but went down-hill rapidly, the gums showing ulceration on the fifth day of admission. Achromycin V 250 mg. q.d.s. was given to alleviate this.

She became progressively anæmic, the white count rising to 160,000/c.mm., 95% monocytes. On the ninth day of admission, she became unconscious with pin-point pupils. Multiple petechial hæmorrhages were present and the bleeding time was 180 minutes. She later collapsed and died.

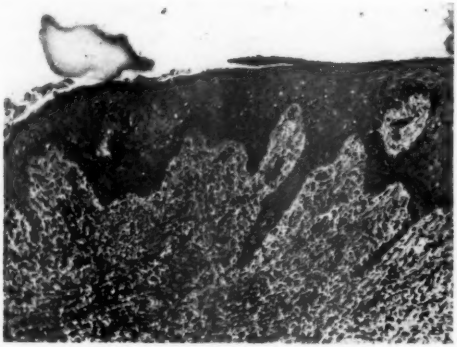


FIG. 2.—Photomicrograph. Gum showing dense infiltration of submucosa by leukæmic monocytes. H. and E. × 125.

Autopsy findings.—(1) Profuse hæmorrhages into most of the organs including a massive cerebral hæmorrhage. (2) Enlargement of all elements of the reticulo-endothelial system, including liver, spleen, tonsils and lymph nodes. (3) Infiltration of many organs with leukæmic cells.

A piece of gum tissue showed microscopically dense infiltration of the submucosa with leukæmic monocytes (Fig. 2).

Acknowledgments.—I am grateful to Mr. R. Sutton Taylor and Dr. K. A. Newton for permission to report this case. To Dr. A. D. Morgan for the photomicrograph, to Dr. J. G. Humble for the blood reports and Dr. P. Hansell for the photographs.

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Section of Comparative Medicine

President—DOUGLAS MCCLEAN, M.B., M.R.C.S.

[*April* 17, 1957]

DISCUSSION ON ARTIFICIAL INSEMINATION

Dr. Margaret Hadley Jackson pointed out that, whereas in animal husbandry artificial insemination was primarily used to conserve and make full use of a valuable sire, in the human field its main use was to overcome barrenness. For this purpose there were two forms of insemination: (1) Donor insemination (A.I.D.=donor) where a fertile donor was needed and (2) husband insemination (A.I.H.=husband) when the husband's semen was used. The two forms have distinct and different clinical uses and their moral and legal implications are also different. For the former, which inevitably is the more controversial, there is a small but steady demand and its four main uses are:

(1) Where the husband is irremediably sterile according to present knowledge or totally impotent (i.e. unable to copulate or to produce an ejaculate).

(2) Where there have been one or more Rhesus tragedies in a family, then a Rhesus-negative donor is indicated.

(3) Where the husband is a carrier of some severe hereditary disability.

(4) Finally, and somewhat theoretically, A.I.D. can be considered as a means of improving the stock by using donors with outstanding mental and physical attributes.

From a total of some 2,500 infertile couples seen during the past twenty-five years only about 200 had needed and asked for A.I.D. but not all had proved suitable. The selection of cases was a difficult and responsible task as also was the building up of a panel of donors. One of the most awkward problems from the doctor's point of view was choosing the correct day in the wife's cycle for doing the insemination. Dr. Jackson summarized the results in 174 couples where A.I.D. had been carried out either with or without the husband's semen being added (*see* Table I). In 85% of the successful inseminations this was done between

TABLE I

	A.I.D.	A.I.D. and H.	Totals
No. of cases	136	38	174
Gave up too soon or went abroad	25	7	32
Failed to conceive after fair trial	39	14	53
Trying now	15	4	19
Have conceived	57	13	70
PREGNANCIES			
Pregnant now	6	—	6
Live birth	56	13	69
Still birth	4	—	4
Miscarriage	10	4	14
Pregnant more than once	17 had 2 pregnancies 1 had 4 „	2 had 2 pregnancies 1 had 3 „	

cycle days ten and fourteen inclusive, the outside extremes being eight and twenty-two. In the majority of cases the day of conception was within 36 hours before or after the change over from low to higher temperature levels on the basal temperature chart. In 3 cases conception occurred more than a week before the "rise"; none occurred more than 48 hours after. In 38 cases the husband was grossly subfertile but not azoospermic and A.I.H was attempted mostly alone at first and then boosted by fertile donor semen or in a few cases boosted from the beginning. Taking this small group first it will be seen that 7 (or one-fifth) of them abandoned the unequal struggle before A.I. had been given a fair trial; 14 (two-fifths) failed to conceive in spite of repeated attempts and another 13 (two-fifths) conceived on one or more occasions (17 pregnancies in 13 women with 13 live births and 4 miscarriages). In the larger A.I.D. group the 136 husbands were azoospermic or homozygous Rhesus-positive with a sensitised Rhesus-negative wife; 25 (less than one-fifth) gave up too soon for various reasons, 39 (rather less than one-third) failed and 57 (well over one-third) have conceived once or more (76 pregnancies in 57 women; with 56 live births, 4 still-births and 10 miscarriages, 6 being pregnant now). Twenty-one couples have asked for A.I.D. to be repeated; 19 have had two pregnancies, 1 has had three and 1 four. It is important to arrange for the same donor if there has been a previous live birth, but it is not invariably possible. The results on the whole are extremely encouraging, the children are well up to the average mentally and physically and, with one exception, the marriages have been consolidated and improved.

Turning to A.I.H., Dr. Jackson pointed out that the indications for this are quite different and include certain forms of impotence, vaginismus, deformity of the sex organs and aberrations of ejaculation; there is also a small group of cases where the semen is oligozoospermic and the sperms are lacking in motility and viability but the volume is adequate (2 ml. or over). The husband can, with practice, learn to divide the ejaculate into two fractions and the first fraction, which usually contains more than 80% of the motile sperm, can then be used for cervical insemination. This can be done either by the doctor using a syringe or by the wife using a plastic cervical cap of one sort or another. This method of collection increases the chances of success with A.I.H. quite considerably. Dr. Jackson went on to discuss the degree of concentration obtained by fractionation—these observations being based on the examination, by Mrs. C. Harvey at Exeter University, of 93 fractionated ejaculates from 21 men. The degree of concentration obtained is shown in Table II; from this it will be seen that 90% of the first fractions show marked superiority over the whole ejaculate, particularly with regard to the number of motile sperm.

TABLE II.—FREQUENCY OF VARIOUS DEGREES OF CONCENTRATION OF SPERM IN 1ST FRACTION

		Ratio of sperm in 1 ml. of 1st fraction of ejaculate (or whole of this fraction if less than 1 ml.) to sperm in 1 ml. of complete ejaculate				
	Number of ejaculates	0·8 1st Fr. inferior	0·8—1·2 No sig. difference	1·21—1·99 Fair concentration	2·0 and over Good concentration	Highest value
All sperm ..	93	8 (8·6%)	16 (17·2%)	48 (51·6%)	21 (22·6%)	3·9
Motile sperm ..	87	3 (3·5%)	4 (4·6%)	41 (47·1%)	39 (44·8%)	4·6

In cases where A.I.H. is being given a trial it is certainly worth asking the husband to collect his semen in two parts if the volume of his complete ejaculate is usually over 2 ml.

It must, however, be recognised that where the total sperm count of the whole ejaculate is only one or two million, or where the motility is very low, putting all the sperm available into 1 ml. of fluid does not greatly increase the chances of success.

There is some indication that, given a reasonably skilful donor, it should be possible to find the optimum volume for the first fraction or, putting it another way, what proportion of the whole ejaculate can most profitably be contained in the first fraction. This may be considerably less than half the total volume and in some men may be as small as 0·25 ml. while in others the first 0·25 or 0·5 ml. of fluid may be composed entirely of prostatic fluid and therefore devoid of sperm and it is not until about 1 ml. goes into the first fraction that a satisfactory concentration is obtained.

see also

JACKSON, M. H. (1955) *Proc. 5th int. Conf. Planned Parenthood,* p. 245. Internat. Planned Parenthood Fed., London.

—— (1957) *Eugen. Rev.*, **48**, 4.

Mr. Reynold Boyd:

Indications for and Techniques of Artificial Insemination in Man

Although artificial insemination (A.I.) is so successful and widespread in veterinary practice it has been little used in man. Most of the current textbooks make little or no mention of it in their sections on sterility. In the treatment of human infertility there are, however, many clear indications for employing artificial insemination, which in suitable and selected cases, yields a high rate of success.

Indications for Artificial Insemination (A.I.H.=husband)

Impotence is an obvious indication. A masturbation specimen can be produced, with few exceptions, even when the failure is due to age. The subsequent pregnancy usually provides a cure in the younger group, in whom the cause is always psychological.

Absent ejaculation which may be classified according to type and cause as follows:

(*a*) Delayed ejaculation in apparently virile or potent young men and

(*b*) Retrograde ejaculation which may be idiopathic or follow endoscopic resection of the prostate.

(*c*) In tabetics where impotence is often an early sign.

(*d*) Following dorsal sympathectomy.

(*e*) In partial or complete paraplegia following accidents to the spine or operation for herniated intervertebral disc.

(*f*) Following denervation of the seminal vesicles in abdomino-perineal resections.

Oligospermia, where the volume is persistently low—in the neighbourhood of 0·25 c.c.—probably due to absent, atrophied or fibrosed seminal vesicles and consequently unresponsive to testosterone therapy.

Oligozoospermia and asthenospermia, making the best possible use of a poor specimen. In this group the failure rate is high but the occasional success justifies the continued use of A.I. In any event, it gives better results than relying solely on stimulatory therapy of dubious value.

Mechanical failure, as evidenced by a negative Huhner test in cases of hypospadias, retroversion, ectropion, fluor vaginæ, etc.

When intercourse is impossible on account of burning vaginal pain in disseminated sclerosis or on account of deformity as in Peyronie's disease, etc.

Indications for Donor Insemination (A.I.D.=donor)

When the husband is sterile or suffers from a grave hereditary disease or from Rhesus incompatibility, donor insemination is indicated if the wife desperately desires a child of her own and the husband prefers to bring up this child rather than any other.

Prerequisites for Donors (1) Between 30 and 40 years old. (2) Fertile with a minimum of morphological defects in the semen. (3) No hereditary disease. (4) Good physical condition. (5) Superior mentality. (6) Matching the husband racially, physically and in aptitudes. (7) Having the same Rhesus factor as the recipient.

Techniques

Self insemination for cases of hypospadias, impotence, dyspareunia and, more particularly, of delayed ejaculation, in which the specimen is collected usually at an inconvenient hour, in a polythene glans bag, moistened with fructose-saline solution. The specimen is drawn up into a nylon syringe and introduced into the vaginal vault by means of an attached piece of polythene tubing. Or the specimen may be injected into a pre-fixed plastic cervical cap through an attached tube. (Fig. 1).



Fig. 1.—The Milex cap. The cap is pre-fixed and the semen is introduced from a nylon syringe through the dependent tube in which there is a bead to prevent leakage.

Standard procedure. The results of A.I. are greatly improved by attention to details such as (*a*) Using plastic containers. (*b*) Mopping out the vaginal vault. (*c*) Aspirating the cervical mucus. (*d*) Leaving the patient in the Trendelenburg position for half an hour.

With regard to aspiration of cervical mucus there are pros and cons. It must be done gently or bleeding will occur making successful insemination less likely. It has been argued that the cervical mucus is protective, filtering abnormal forms and infection—but I do not believe that abnormal forms have fertilizing powers nor that ascending infection is ever caused by removal of the mucus *per se*.

The cervical canal is cleared by aspiration and with the help of weak bicarbonate solution or Alevaire and then filled with semen, any excess being put into the vaginal vault. The patient is left in the head-low position for 20–30 minutes with legs crossed except in some obese subjects in whom this produces fluor vaginæ. Indeed at times it is best to leave the speculum in situ so as to be certain that the os is bathed in semen.

Intra-uterine insemination is unwise as it frequently causes severe uterine cramps and there is a real possibility of introducing infection with a resultant salpingitis.

Intra-cervical insemination is the method of choice when using the *split specimen technique.* The first, smaller fraction of a masturbation specimen usually contains a much higher density of sperms of a much higher percentage motility than the second, larger fraction; indeed some 80% of the total number of spermatozoa will be found in the first half of the ejaculate. Sometimes the density is five times as great. But when, through anxiety or at the initial attempt, this first portion is kept too small it may be made up almost entirely of prostatic secretions in which very few spermatozoa will be found.

When using a small volume specimen or a split specimen, the cervical canal should be filled to "bulging" but not allowed to overflow or the contents will be siphoned out.

The results of the split specimen method are very encouraging and show that it is a major advance in the handling of the subfertile male. This technique has now replaced centrifuging which concentrates debris as well as sperms and markedly reduces the viability of an already deficient specimen.

In some 10% of cases of oligozoospermia and asthenospermia, however, there is no significant difference between the two fractions and in these cases cap insemination is the method of choice.

Cap insemination (*C.A.I.*) allows the whole ejaculate (or up to 4 c.c.) to be kept in contact with the external os for 6 or more hours. It is eminently suitable for some cases of oligozoospermia and asthenospermia, for pin-hole os, etc. It is amazing how often a pin-hole os can be dilated and still remain the same! Fluor vaginæ is also an indication; this condition has long been discounted as a cause of infertility but the longer fertile semen is in contact with the external os at the right date the greater the certainty of a pregnancy.

Asthenospermia is usually associated with great increase in volume—from 6 to 10 c.c. In many cases the first part of a split specimen shows no advantage in numbers but if the specimen is produced in two approximately equal portions the first will be found to contain most of the active spermatozoa; and it is this half that is used for C.A.I.

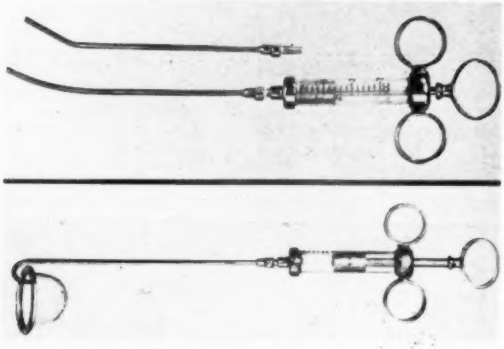


FIG. 2.—Above: syringe and cannula for intra-cervical insemination.
Below: Plastic cap and crooked cannula for C.A.I.

The Milex cap with its attached tube for easy filling can be used but the crooked cannula technique is preferable (Fig. 2).

The procedure is as follows: The vagina and cervix are exposed and cleansed by dry mopping. No lubricant is used. The speculum is removed. A plastic cap of 28 to 30 mm. size is inserted into the vagina and pushed on to the cervix before reinserting the bivalve speculum through which it is, unfortunately, too large to be introduced. The cap is now held firmly in place with the help of bullet extracting forceps, while the crooked cannula is brought down between the cervix and the rim. The semen is then introduced and will be seen to rise and cover the external os. The cap is left in place for six hours or longer. A strong thread can be attached to the rim to facilitate removal but on the first occasion it is wise for the patient to return to the clinic so that leakage can be excluded.

For all these methods it is best for the semen to be not more than 1 hour old but I have had a success at 5 hours in a patient who brought the specimen from Worcester to London and much longer time-lapses are recorded.

Special techniques are required for cases of absent ejaculation.

(i) *Retrograde ejaculation* due to neuromuscular imbalance is easier to deal with than when it follows endoscopic resection of a prostatic bar. After a salt-free diet for forty-eight hours and restricted fluids for twenty-four hours the patient empties his bladder and then attempts to produce a specimen, part of which can easily be collected for insemination from the prostatic urethra by means of a Guyon posterior urethral metal cannula.

(ii) *For retrograde ejaculation* due to altered mechanics following endoscopic resections a different technique is required. The bladder cannot be emptied completely nor is there an integral prostatic urethra. In these cases the urine must be

(*a*) dilute. (*b*) strongly alkaline—pH 7·4.

An alkaline mixture and free bland fluids are given for twenty-four hours. The bladder is "emptied" normally. It is useless to expect a patient to be able to "produce" a specimen immediately after catheterization so a certain amount of dilute residual urine must be accepted. A plastic catheter is passed into the bladder and urine is withdrawn. The latest fraction will be the least diluted semen and on examination density will be found adequate for artificial insemination and progressive motility unimpaired.

In many of these cases spermatozoa will be found in spite of recurrent attacks of bilateral epididymitis. The depressant effect of sulphonamides on spermatogenesis should be remembered and precautionary antiseptic or bacteriostatic therapy is best interrupted for several weeks prior to attempting A.I.

(iii) *Absent ejaculation* often occurs after dorsal sympathectomy for hypertension.

Semen can only be expressed by vaso-vesicular massage, the resultant specimen being all too frequently only minimal in quantity and quality. Even if a satisfactory volume is obtained a great proportion of the sperms will be found to be aged and immotile. The same difficulties arise in some cases of complete impotence where the only ejaculations are in the form of unpredictable night-losses and also in cases of psychological absent ejaculation subject to the same losses.

Vaso-vesicular massage to yield results must be meticulously performed and should be distinguished from the V.D. clinic procedure of taking a prostatic bead. It must be remembered that the vesicles are freely mobile and carry the vasal ampullæ with them. The stripping should be done with a broad movement of the index finger which suddenly descends on the vesicle "unawares" and sweeps inwards and down to the centre line. Finally the prostatic and posterior urethra are emptied by pressure between finger and thumb.

Electrical stimulation of ejaculation should be possible in all these cases. It is most successfully applied to rams and the technique is easily applicable to man. A sine type wave is used, the leads being attached to small electrodes placed on either side of a ring or thimble worn at the end of the right index finger, which is introduced per rectum and placed as nearly as possible over the vasal ampullæ. Care must be taken to avoid trauma to the anal mucosa and if there is difficulty a speculum should be used. After insertion the ring can be easily recovered and slipped on by pulling on the leads. The current must be kept on for up to twenty minutes at times and several attempts may be needed to educate the musculature involved.

(iv) When absent ejaculation follows perineo-abdominal excision of the rectum (which has sometimes to be performed in quite young men) massage is impossible. Here one must

resort to the forming of a vaginal spermatocele (seminal "hydrocele") from which spermatozoa can be withdrawn at times suitable for A.I. (Fig. 3).

(v) Attempts have been made in paraplegics to produce an erection and ejaculation by means of an intrathecal injection of prostigmine. In my hands this has not been popular enough to repeat as patients complain of the painful erections and of the subsequent headache. If spermatozoa can be found in the vesicular bead indicating that the inevitable repeated attacks of epididymitis have not yet blocked the tubules or vas then vaso-vaginal

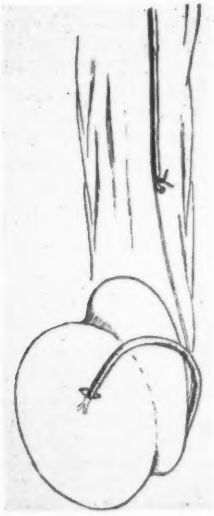


FIG. 3.—Vaso-vaginal implantation.

implantation is indicated. It can be performed without anæsthesia and healing is uncomplicated. It should be added that pregnancies have followed insemination of progressively motile sperms recovered from spermatoceles in spite of the current maturation theories.

The timing of ovulation.—Many of the methods of accurately timing ovulation have a post hoc connotation and are beyond the laboratory facilities of the busy specialist. For all practical purposes temperature recordings are sufficient, the assessment being confirmed by the appearance of the cervical mucus, by spinnbarkeit, and by a positive palm leaf (Arborization) mucus test. In my own cases, 83% of success has followed insemination on the morning of the temperature drop or before the biphasic rise, 5% from A.I. two days before the rise, 10% on the top of the rise and 2% the day after the rise.

These figures are not really strictly comparable and are only meant to indicate that conception can and does arise from insemination well on either side of what is the most favoured date.

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Section of Otology

President—PHILIP J. JORY, D.S.O., F.R.C.S.

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The Principles and Practice of Bone Conduction Audiometry: A Review of the Present Position

By J. D. HOOD[1]

WHEREAS the technique of air conduction audiometry is well established, the basic principles of bone conduction audiometry are still far from being generally understood. In consequence, the tests are still too often inefficiently performed, and hence fail to provide the vital diagnostic information which is their purpose.

As will be shown, this disappointing state of affairs is quite unnecessary, and requires for its correction no more than a rational standardization of our technical equipment and test procedures, whereby proper use is made of the considerable body of acoustic and physiological knowledge now at our disposal.

An essential requirement with all bone conduction tests is the exclusion of the untested ear by means of an efficient masking sound, so that all threshold readings can be validly related to the tested ear. In order to understand how this requirement arises, we need to know, firstly, certain facts concerning the transmission of air and bone conducted sounds across the head; and, secondly, the physical characteristics of a sound which confer upon it maximum efficiency for the masking of pure tones of specified frequency.

The facts relating to sound transmission across the head are conveniently studied in subjects with normal hearing in one ear and complete deafness of the other.

The results obtained are shown in Fig. 1. The calibrated columns are taken to represent the available hearing capacity of each ear; the solid column at the left represents total deafness of

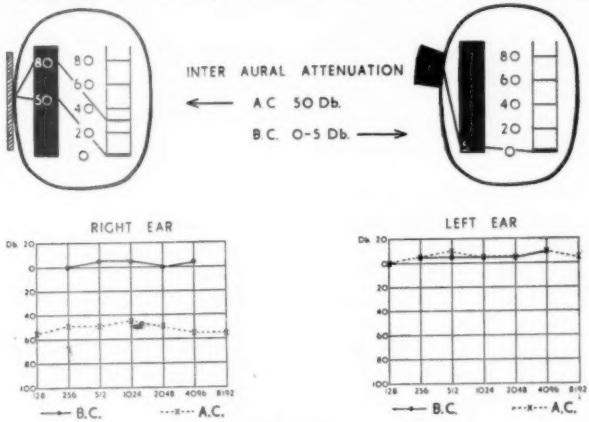


FIG. 1.

the right ear. If an air-conducted sound of 50 db. is applied to the right, or deaf ear, it will be heard in the left ear at threshold intensity. Similarly, a sound of 80 db. applied to the right ear will be heard in the left ear at a level some 30 db. above threshold. The reason for this is that sound from an air conduction receiver is transmitted across the skull with an inter-aural attenuation of the order of 50 db. By contrast, the inter-aural attenuation for sound from a bone conduction receiver applied to the right mastoid is negligible, and the sound will be heard at the left ear with a loss of only a few decibels.

In the lower half of Fig. 1 are shown the pure tone audiograms of the right and left ears for air and bone conduction carried out without masking. They indicate normal hearing for the left ear, and a severe conductive deafness for the right ear. In agreement with this, the classical tuning fork tests applied to the right ear lead us into that well-known pitfall of

[1]From the Otological Research Unit, Medical Research Council, National Hospital, Queen Square, London, W.C.1.

clinical practice, the false negative Rinne. In fact, for the reasons given, the threshold readings, both for air and bone conduction, obtained for the right ear and shown in the audiograms, are false readings derived from the left or untested ear. In the case of air conduction, owing to the comparatively high inter-aural attenuation of 50 db., such false readings are only obtained when the stimulus intensity exceeds this level. Clearly enough, true readings would result with any degree of deafness of the right ear below this level.

Hence the rule that when the difference in the air-conduction thresholds of the two ears exceeds 50 db. the readings for the worse ear cannot be relied upon, unless the better ear is excluded by masking.

In the case of bone conduction, however, the situation is much more difficult. Here the inter-aural attenuation is negligible, and hence, if the bone-conduction threshold of the right ear be raised by any amount above 5 db., a receiver on the right mastoid will give false normal readings derived from the opposite untested ear. Hence the rule that *all* bone conduction tests require the exclusion by an air-conducted masking sound of the untested ear. A variety of masking noises has been devised to serve this purpose. A few, like those

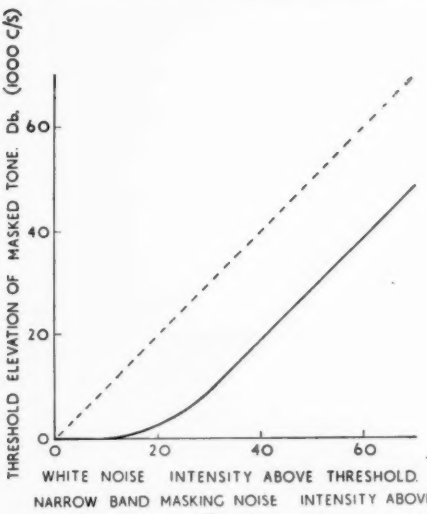


FIG. 2.

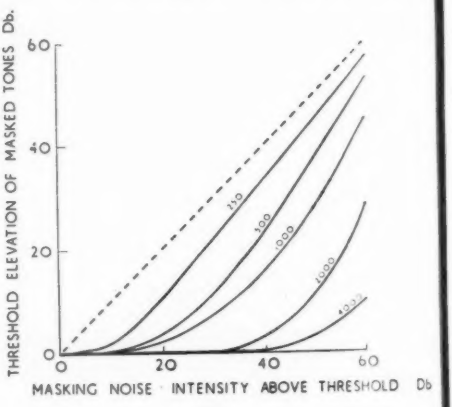


FIG. 3.

described by Zwislocki (1951), or Denes and Naunton (1952), are efficient, but of the majority it can only be said that they raise the threshold of the masked ear in some vague unspecified manner.

In order to understand what makes a masking sound efficient, it is helpful to consider first the masking of pure tones by white noise, that is to say, noise having a flat frequency

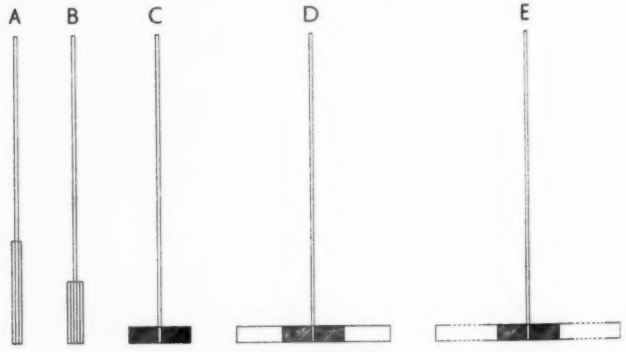


FIG. 4.

spectrum covering the whole audible frequency range with equal sound energy per cycle. In Fig. 2 is shown the elevation of the threshold of a pure tone of 1,000 cycles in the presence of white noise. The noise intensity is expressed in decibels above normal threshold, and it will be seen that below the 20 db. level it produces negligible masking of the pure tone. Above this level there is an incremental equivalence in decibels of masking and of masking

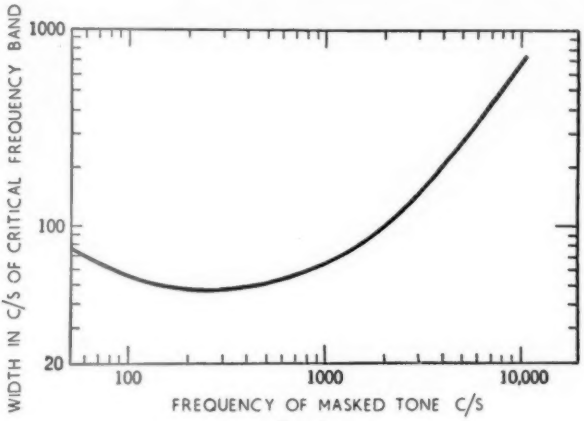


FIG. 5.

noise intensity. At any masking level, therefore, the loudness of the white noise will be much in excess of the pure tone, since its intensity will at all times be some 20 db. higher.

This brings us to the first important requirement of a masking noise, namely, high masking efficiency which Denes and Naunton have defined as "good masking ability, but minimal loudness". Clearly, white noise does not conform to this ideal. Nevertheless, it is superior to some of the masking noises incorporated in many commercial audiometers. A typical example is shown in Fig. 3. The masking noise is modified mains hum, its intensity level in decibels above normal threshold is shown on the horizontal scale, and on the vertical scale the resulting threshold elevation of various pure tones. It will be seen that for frequencies above 1,000 cycles masking is grossly inefficient. At 2,000 cycles no masking at all is produced below an intensity level of some 50 db. at which point it is already becoming unpleasantly loud to the subject.

Having considered these examples of inefficient masking sounds, we will consider next how we set about our task of designing what we really require, that is to say, sounds which have the maximum possible efficiency for the masking of the limited range of specified pure tones, which are conventionally used for bone-conduction audiometry. Here, as usual, we turn for guidance to some of Fletcher's (1940) early work upon frequency discrimination, loudness and masking, which led him to define the existence of certain so-called critical frequency bands. Their significance lies in the fact, firstly, that in any masking noise only those frequencies within a certain critical band centred around the pure tone contribute to its masking, and secondly, when the tone is just audible against the background of noise, the total acoustic power of the components within the band is the same as that of the pure tone. The principles are illustrated schematically in Fig. 4. This shows noise bands of varying widths centred about a single pure tone which is just audible in their presence. The acoustic energy, both in the bands and in the pure tones, is represented by the enclosed area of each. Band A is only three cycles wide, and since its total energy is the same as that of the pure tone, the energy per cycle of the noise is only one-third that of the pure tone. Band B is five cycles wide. Once again, its total energy is the same as that of the pure tone, which thus has five times as much energy as each cycle of the band. The width of Band C is that of the critical band, and yet again the total energy in the band is equal to that of the pure tone.

In bands D and C the noise spectrum extends beyond the critical band, so that the total energy of the bands is much increased. Since, however, it is only the energy in the critical band which contributes to the masking, these noise bands possess no greater masking power, and the energy level of the just masked pure tone remains the same. In other words, those components outside the critical band, while they may have the effect of making the noise

very much louder, contribute nothing to its effective masking power. This provides us with the theoretical basis for the concept of high masking efficiency; clearly our first objective must be to remove as much as possible of these unnecessary components.

Are we likely to gain anything from the use of band widths which are only a fraction of the critical band, as for example in Band B? Apart from the fact that to do so would present very difficult technical problems of sound filtering, we should gain nothing in efficiency and, in addition, would be faced with the added difficulty of the tonal similarity of the pure tone and the masking noise which might result in some confusion to the patient. If, however, the band width of the masking noise is extended to correspond roughly to that of the critical band, as in Band C, then we find that though masking sound and pure tone are identical in pitch, they are still readily distinguishable, and hence are not confused by the subject tested.

The critical band widths for the various frequencies are shown in Fig. 5. As will be seen, they are of the order of only a hundred cycles wide. It would be technically impossible to produce noise bands to these specifications, nor, as will be shown, is this necessary.

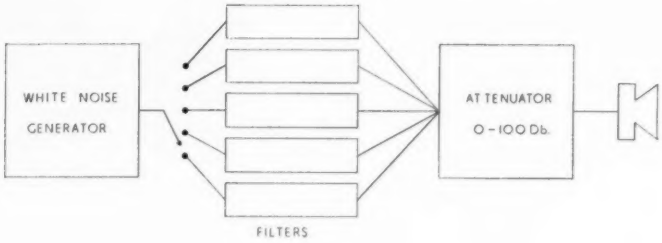


FIG. 6.

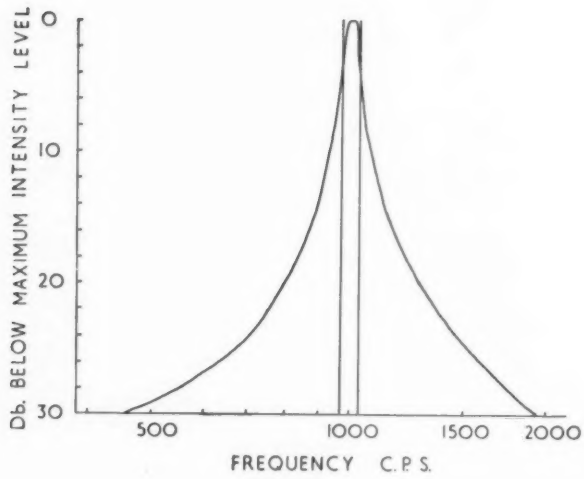


FIG. 7.

In Fig. 6 is shown schematically the equipment we have used for obtaining narrow bands of noise, having the masking efficiency required. A white noise generator is followed in turn by a number of filters of high selectivity centred around each of the pure tones normally used in bone conduction audiometry, followed in turn by an attenuator calibrated in steps of 10 db. Each of the filters can be selected by means of a switch, and passes only a very narrow band of frequencies.

The selectivity curve for the band centred at 1,000 c/s, which is typical of the other curves, is shown in Fig. 7. At the centre, the two vertical lines give the measure of the width

of the critical band. The curves extend somewhat beyond the critical band at the base; nevertheless, the maximum energy in the band is centred within the two parallel lines.

The dotted line in Fig. 2 illustrates the high masking efficiency obtained with this band.

In contrast to the masking effect of white noise, there is 100% masking efficiency. The curve begins at zero, and there is an exact one-to-one relationship between noise level and masked threshold. Thus, if the noise is raised 20 db., the pure tone threshold is raised by an identical amount, and so on. All the noise bands are similar in this respect, and we regard it as one of their most important features. Thus, if it is desired to raise the threshold of a pure tone by, say 40 db., it becomes a simple matter of raising the intensity level of the noise band by exactly the same amount. The practical importance of this is best illustrated by considering the simple application of these noise bands to the technique of bone conduction tests.

Fig. 8 is a schematic illustration of the rationale of the procedure employed at the Otological Research Unit, and referred to for convenience as the "shadowing" technique. Let there be a pure nerve deafness of 40 db. of the subject's right ear to be tested, and no loss of hearing of the left ear. As before, the columns on each side are taken to represent the available hearing, and are calibrated in decibels. The solid portion of the left column represents the nerve deafness of the right ear. A bone conducted sound at normal threshold intensity applied to the right mastoid is heard in the subject's left ear. This provides us with the first point on the graph shown below, in which the masking intensity at the left ear is plotted on the horizontal scale and the bone-conduction threshold responses on the vertical scale.

Now, as shown in Fig. 8, the masking noise at a level of 10 db. applied to the left ear

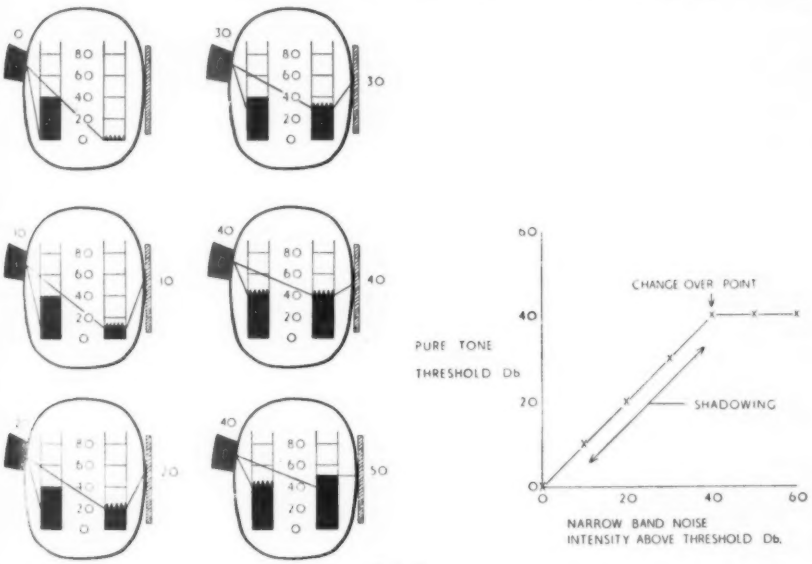


FIG. 8.

raises its threshold for the bone conducted test tone by 10 db. In the same way, increases in masking noise intensity of 20 or 30 db. will bring about increases of identical magnitude in the threshold values for the test tone. Reference to the graph shows, up to this point, this step by step correlation, the "shadowing" effect between the intensities of masking noise and test tone thresholds. When, however, the masking noise reaches the 40 db. level it will be seen that the bone conducted test tone will be heard at threshold by the right as well as the left ear. A further intensity increase of the masking noise to 50 or 60 db. will further raise the threshold of the left ear alone, leaving the test tone to be heard by the right ear alone without further elevation above its true threshold value, 40 db. The true threshold for the right ear will thus be shown at a point on the graph, referred to as the "change-over" point, at which the slope of the curve changes from 45 degrees and becomes horizontal. In the case being considered, the change-over point occurs at 40 db. If, extending the

argument, the deafness of the tested ear had been 50, 60 or 80 db. identical values of masking noise intensity would have been required to reach the "change-over" points. In all cases, true threshold readings would be obtained.

The essential steps of the test procedure are thus:

(1) The demonstration of the "shadowing" effect. This establishes that both masking noise and test tone are confined to the untested ear.

(2) The identification of the "change-over" point. This establishes the true threshold of the tested ear.

The case analysed in Fig. 8 is one of comparative simplicity in that the unilateral deafness was of the "nerve" type. In unilateral deafness of the conductive type, however, we are confronted with a situation of considerably greater difficulty. This arises, as will be shown, from the fact that the inter-aural attenuation of an air-conducted masking sound does not exceed some 50 db.

The situation is illustrated in Fig. 9.

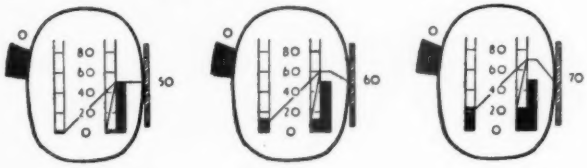


FIG. 9.

Here, the subject has normal hearing of the right, or tested, ear, and a pure conductive deafness of 50 db. of the left ear. This is indicated by the solid area adjoining the calibrated column which represents the inner ear hearing capacity of the left ear.

In ascertaining the bone-conduction threshold of the right ear we must, as usual, apply an air-conducted masking noise to the left ear. Here a serious difficulty arises, since before this noise can become effective its intensity must reach 50 db., the amount of the conductive deafness. At this intensity it will just overcome the inter-aural attenuation for air-conducted sound, and begin to exert a masking effect upon the right ear as well as the left. If the intensity of the masking noise be further increased in steps of 10 db., a "shadowing" effect will occur, and the bone-conduction thresholds, derived equally from the two ears, will rise *pari passu*. In this instance, however, the "shadowing" effect will continue indefinitely, and no "change-over" point will be reached.

The underlying difficulty is clearly to be found in the fact that the inter-aural attenuation of the air-conducted masking noise has a limit of some 50 db. What is needed, therefore, is some means of extending this limit, and providing a zone of masking noise intensities which will be above the air-conducted threshold of, and at the same time confined to, the left ear. Within this zone, the "shadowing" procedure could be applied, and the absence of a "shadowing" effect would then prove that bone-conduction threshold readings were derived from the right ear, and could be accepted as valid.

The manner in which such an increase of the inter-aural attenuation can be accomplished stems from a brief report on the use of insert receivers which appeared in the Report of the Electro-Acoustics Committee "Hearing Aids and Audiometer", 1947. In this it was

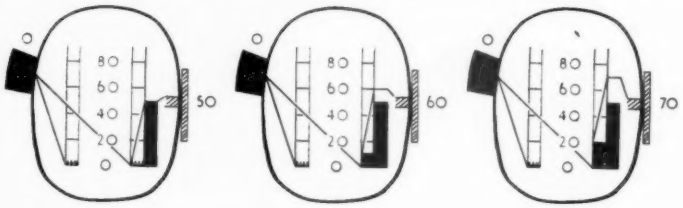


FIG. 10.

suggested that the acoustic linkage between the two ears which occurs when any air conduction receiver is used arises from the vibrations imparted to the skull at the air-bone interface bounding the receiver. Both Littler *et al.* (1952) and Zwislocki (1953) have carried out further studies, and it has been shown that the vital factor affecting the attenuation is

the area of the receiver in contact with the head. Thus, the smaller the area the greater the attenuation, and in the limiting case when an insert receiver is used, thus presenting the smallest possible surface to the skull, the inter-aural attenuation increases to a figure as high as 90 db.

As Littler *et al.* (1952) so ably pointed out, the practical importance of this finding is considerable, making possible as it does the accurate determination of bone-conduction thresholds in the presence of conductive deafness well beyond the limit of 50 db. This is illustrated in Fig. 10. Masking noises of intensities up to 90 db. are applied to the left ear by means of a rubber-tipped-insert receiver without fear of cross conduction to the right ear.

Thus, at any intensity between 50 db., the air-conduction threshold of the left ear, and 90 db., the masking noise will be effective in the left ear alone. If we now apply the "shadowing" procedure, and make step by step changes of masking intensity within this range, they will be found to leave unaltered the bone-conduction threshold readings. In other words, the "shadowing" effect is absent, and the threshold reading, 0 db., can be accepted as valid for the right ear.

When the deafness is bilateral, and of the mixed conductive and nerve type, bone-conduction tests may be greatly complicated, and indeed it is only within certain limits that accurate results are then obtainable.

An audiometrician needs to know what these limits are, and it is fortunately possible to define them with reasonable accuracy. The situation is analysed in the cases shown in Fig. 11 (A, B and C). In 11A the subject has a nerve deafness of 60 db. of the right ear and conductive deafness of 30 db. of the left ear. In order to establish the bone-conduction threshold of the right ear, the usual masking noise must be applied to the left, and owing to

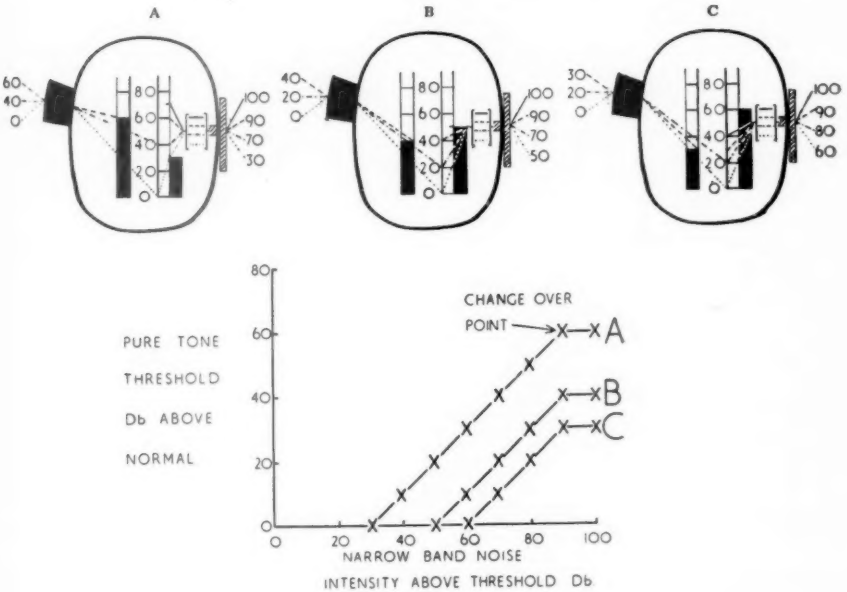


FIG. 11.

the conductive deafness its minimum effective intensity will be 30 db. Above this point shadowing will occur, as shown in the graph (A). That is to say, both masking noise and test tone will be confined to the left or untested ear. When the masking intensity reaches the 90 db. level, its true masking effect upon the left ear will be restricted to 60 db. by the conductive deafness and the test tone will now be heard at threshold in the right ear as well as in the left. This is the critical change-over point, and beyond it a further increase of masking intensity to 100 db., the maximum practicable level, will raise the threshold of the left ear by a further 10 db. while leaving unaffected at 60 db. that of the right ear. This, therefore, will be its true threshold.

Two factors determine the results thus obtained. Firstly, 100 db. is accepted as the

maximum intensity of masking noise which it is practicable to use for clinical tests. With this the critical change-over point occurs at a level 10 db. lower, 90 db., and to this is convenient to refer as the maximum critical masking intensity. Secondly, the threshold of the tested ear can be determined only if it lies at or below the level of masking induced by the maximum critical masking intensity in the untested ear.

Now, in the case 11A this level is reduced by 30 db., the amount of the conductive deafness and hence, 60 db. is the maximum measurable elevation of the bone-conduction threshold of the right ear. From this we may derive the limiting formula:

Maximum measurable bone-conduction threshold=90−conductive deafness (db.) of opposite ear.

The application of the test procedure to the three cases A, B and C, represented in Fig. 11, is shown in the graph.

In all three the amount of the nerve deafness of the tested ear is the maximum measurable according to the limiting formula. Thus:

Case A 60 db. (90–30)
Case B 40 db. (90–50)
Case C 30 db. (90–60)

In each case the true threshold is given by the change-over point which occurs at the maximum critical intensity, 90 db. of masking noise.

Although for simplicity of explanation the cases shown in Fig. 11 have been selected to exhibit conductive deafness alone of the untested ear and nerve deafness alone of the tested ear, accurate bone-conduction tests are still possible within the limits of the formula when the deafness, of either one or both ears, is of the mixed type. This is illustrated in Fig. 12. In the right ear there is a conductive deafness of 40 db. with a nerve deafness of 60 db. The air-conduction audiogram thus shows a loss of 100 db. In the left ear there is a conductive

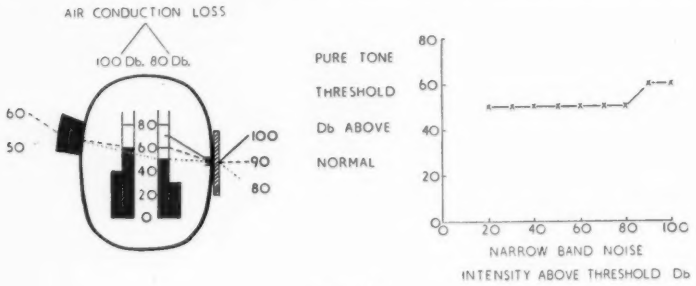


FIG. 12.

deafness of 30 db. with a nerve deafness of 50 db. The air-conduction audiogram thus shows a loss of 80 db. With no masking noise applied to the left ear the bone-conduction threshold reading is 50 db. derived, in fact, from the left ear, though this cannot be specified at this stage of the test.

This reading remains constant with increase of masking noise intensity up to 80 db. With the masking intensity increased to 90 db., however, and still confined at this level to the left ear, the threshold reading is increased to 60 db. and remains unchanged when the masking intensity is further increased to 100 db. As shown in the graph, "shadowing" occurs between the 80 and 90 db. levels of masking noise intensity with the "change-over" point at 90 db. It follows that up to the 80 db. level of masking noise intensity, the threshold reading, 50 db., must be derived from the left ear. Further, that at and above the 90 db. level, the threshold reading, 60 db., is derived from the right ear. Subtraction of these bone-conduction losses from the air-conduction losses gives the amounts of the conductive deafness, thus:

Right ear 100–60=40 db.
Left ear 80–50=30 db.

In each case, the amount of the nerve deafness is the maximum which can be measured according to this formula. Thus for the right ear:

60 db. (amount of nerve deafness)=90–30 (amount of conductive deafness of left ear).

For the left ear:

50 db. (amount of nerve deafness)=90–40 (amount of conductive deafness of right ear).

As will be seen from the foregoing analyses, the use of the maximum efficiency masking

technique described in this communication brings within the resolving power of air and bone-conduction audiometry all but the few exceptional cases which lie beyond the bounds of the limiting formula.

In all cases, however, careful attention should be given to the fundamental features of the test procedure which is outlined as follows:

(1) Establish the air-conduction audiogram of both ears in the normal way with masking, if necessary, of the untested ear, i.e. when the difference in the hearing loss between the two ears exceed 50 db.

(2) Find the bone-conduction threshold with the bone-conductor applied to the mastoid of the tested ear without masking of the untested ear.

(3) Apply the masking noise of the appropriate band to the untested ear by means of an insert receiver and find a bone-conduction threshold reading.

(4) Apply the "shadowing" procedure thus: Increase the level of the masking noise by 10 db. above threshold and re-test the bone-conduction threshold. If the bone-conduction threshold is raised by 10 db. increase the masking intensity by another 10 db. and repeat. Continue this procedure until the point is reached at which the bone conduction remains constant with further additional incremental steps of 10 db. of the masking noise. This is the "change-over" point, and gives the true bone-conduction threshold of the tested ear.

Suggestions for the improvement of standard equipment tend to encounter two kinds of objections. Firstly, that they involve excessive technical difficulties. Secondly, that the solution they offer is far from complete, and hence further development should be awaited. Neither of these objections appears to be applicable in the present situation. No serious difficulties attend the generation or application of the masking sounds described, and as for further developments, these cannot be expected since in many respects the efficiency obtained is 100%, at which level an ample reserve is provided for the attainment of practically all the clinical results which are required. It is, therefore, to be hoped that the methods described will find useful application in improving the design of standard audiometric equipment.

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Recent Work on the Biochemistry of the Labyrinthine Fluids

By L. CITRON[1] and D. EXLEY[2]

THE search for new knowledge of the endolymph has received a strong impetus from the evidence, spectacular but still unexplained, of its circulatory derangement in certain important diseases of the mammalian inner ear, among them Ménière's disease and the Scheibe type of hereditary cochleosaccular degeneration. In the course of earlier work much has been made of the abundant morphological data at our disposal, but their value is clearly limited when we come to apply them to the problems of the origin, flow and absorption of a fluid of unknown function and composition. Thus, Shambaugh's (1908) observation of the cellular structure of the stria vascularis led him to attribute thereto the secretion of the endolymph. But his arguments could not be regarded as conclusive, and much the same must be said of the studies of Secretan (1944) and others who have interpreted certain histological appearances in the saccus endolymphaticus as evidence both for and against its absorptive function. Nor have experimental methods been entirely neglected, and Guild's (1927) use of the Prussian blue granule technique led him to conclude that a flow of endolymph took place from the scala media by way of the saccule to the saccus endolymphaticus, whence it was absorbed into the radicles of the surrounding venous sinuses. However, the technical difficulties of these experiments were great and, so far as we know, they have never been repeated.

This conflict of evidence has long made apparent the need for new and more penetrating methods of investigation, and the present contribution is concerned with the application to the problems of the endolymph of modern methods of micro-chemical analysis. The history of the subject is very short. In 1940, Aldred, Hallpike and Ledoux described a method for

[1] From the Otological Research Unit, Medical Research Council, National Hospital, Queen Square, London, W.C.1.
[2] From the Cell Metabolism Unit, Medical Research Council, Department of Biochemistry University of Oxford, South Parks Road, Oxford.

the collection from the scala media of the cat of small samples of endolymph, which they used for the first estimations of its osmotic pressure. Ledoux (1941, 1943, 1950) later used this method in his studies of the chemical and physical properties of the labyrinthine fluids. It is, however, to Smith, Lowry and Wu, of Washington (1954) that we owe the first detailed account of any measurements carried out by means of modern micro-chemical techniques of the electrolyte contents of the mammalian labyrinthine fluids, and the primary purpose of the present investigation has been to repeat and extend their observations. One of us (L. C.) carried out the collection of the labyrinthine fluid samples; the other (D. E.) was responsible for their microchemical analysis.

Methods

A. Collection of Fluid Samples

The essential step in the collection of the samples has been the insertion of fine glass pipettes into the endolymph system of the cat and guinea-pig. These pipettes were made of boro-silicate glass, and were especially drawn in the laboratory. It was found necessary that the pipette tips should have an outside diameter within the range 50 to 100 microns. Penetration was difficult with larger tips, whilst smaller tips did not permit the passage of the perilymph samples. Endolymph samples were easier to obtain from the cat by passing the pipettes through the round window membrane. After removal of this membrane, a finer pipette was then introduced into the endolymph-filled scala media, through the basilar membrane (Fig. 1).

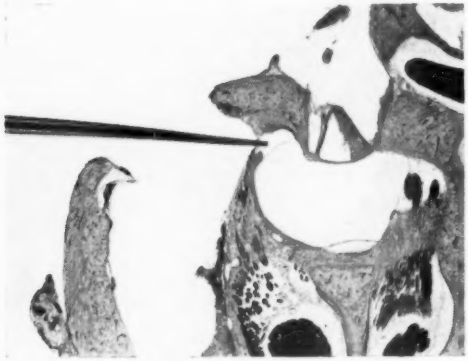


Fig. 1.—Collection of endolymph from cochlea of cat.

In the guinea-pig, specimens of the perilymph were obtained by passing the pipette either through the round window membrane, or else through the thin ligament around the stapes foot-plate. The stapes was then removed, and endolymph collected from the utricle in the manner of Smith *et al.* (1954) (Fig. 2).

The operation was conducted under Urethane anæsthesia. The head of the animal was firmly immobilized by means of a clamp attached directly to the skull. The pipettes were carried upon a micro-manipulator working under 10 x magnification of a Leitz dissecting microscope. Contamination of the specimens with blood was a serious difficulty, and constant suction was necessary throughout the operations to avoid it. All specimens were drawn up by suction into the collecting pipettes, which were then heat-sealed at both ends and immersed in Terpineol. This oil has a refractive index very similar to that of glass, and examination of the immersed pipette under a high powered microscope readily revealed the presence of red blood cells in the specimen. All specimens containing more than a few red cells were discarded. The sealed pipettes found to contain satisfactory specimens were then packed in vacuum flasks, filled with CO_2 snow, and despatched to the Department of Bio-chemistry at Oxford.

B. Microchemical Analysis.

The maximum amount of endolymph obtained was 0·5μl., generally about 0·2μl. This is about 1/1000th of the amount usually taken for a blood count. On a microscope slide 0·2 cl. forms a drop which will approximately cover a typewritten full stop. For various reasons these very small samples cannot be pooled, and new methods have been required for their analysis.

By comparison with those required for the usual micro-methods of analysis the volumes

of our fluid samples are less by one-thousandfold, calling for the estimation of millimicrograms instead of micrograms. Estimations have been carried out of the inorganic ions, sodium, potassium, calcium, magnesium and chloride. Protein and non-protein nitrogen estimations have also been made. In addition, the finding by Jensen and Vilstrup 1954 of an apparently high concentration of hyaluronic acid in the endolymph of certain dogfish has led us to carry out estimations of its concentration in the labyrinthine fluids of the guinea-pig.

For work on the inorganic ions flame photometry was used. With this method an aqueous solution of the sample is atomised in a flame in which the elements all emit their characteristic spectra. This light is then passed via an optical system which can be arranged to select the spectrum of the desired element only. This selected light band then falls on a photosensitive cathode of a photoelectric cell, which converts it to current which can be read on a meter. The Beckman flame photometer is the most sensitive instrument available commercially, and can be used with either an oxy-hydrogen or an oxy-acetylene flame, which with aqueous solutions give temperatures of about 2,500° C. The current is amplified by means of a photo-multiplier, the instrument having an overall amplication of about 300,000. Readings are taken on a potentiometric scale, and are produced by operating a potentiometer to balance out the current produced by the element with the aid of a null point meter.

The time taken to obtain a reading, using this instrument, is about 30 sec. and in this time 1 ml. of solution is atomized. Thus, to obtain a reading, it is necessary to dilute a

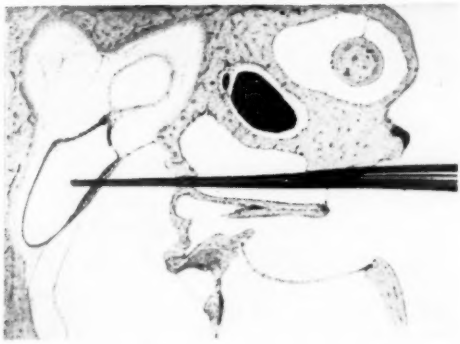


FIG. 2.—Collection of endolymph from utricle of guinea-pig.

0·2μl. sample 5,000 times. This very sensitive instrument was, however, not sensitive enough to measure most elements in our own samples at the required millimicrogram level, particularly such weakly emissive elements as magnesium.

Efforts were, therefore, made to increase the emission of inorganic ions, and it was found that the hotter the flame used, the greater the sensitivity. Using one of the hottest flames possible produced by burning 90% acetone in 5% HCl in an oxy-hydrogen flame (here the temperature was about 3,500° C.) it was found possible to increase the emission of calcium and magnesium about 50 times. In this flame our samples, 0·2–0·5μl. diluted to 0·1 ml., were atomized in 3·5 sec. The flame photometer was modified so as to increase its sensitivity and speed of operation. Thus, the photo-multiplier was operated with very high dynode voltages to increase the current. The circuit was also changed so that this current charged a condenser, its discharge current through selected known resistors being then read directly on a sensitive galvanometer or on a recorder. Instantaneous readings could, therefore, be taken and less material was required. The instrument had an overall amplification of about 50 million with semi-automatic operation. Graphs were constructed using standard amounts of elements against times of discharge to known arbitrary levels fixed on the recorder. From these graphs unknowns were readily calculable. Improved in this way the equipment proved to be about 1,000 times more sensitive than the original Beckman instrument and it was possible to detect a ten-billionth (1×10^{-12}) gram of sodium.

Investigation of the hyaluronic acid content of the labyrinthine fluids was carried out using the technique of absorption spectro-photometry. The approach was an indirect one, and the concentration was established not of the acid itself, but of one of its derivatives, hexosamine. For this a new colorimetric procedure was developed. The hexosamine was separated from other sugars by shaking with a few grains of an ion exchange resin. It was then de-aminated to produce a compound which reacts with pyrrole to give a yellow colour. The absorption of this yellow colour was measured by absorption spectrophotometry with

the use of special ultra-micro-capillary cells. These cells hold only 0·1 ml. of liquid and possess a 5 cm. light path, and are possibly the most sensitive absorption cells yet used.

Results

The results of previous analyses of the cerebrospinal and labyrinthine fluids of the cat and guinea-pig are shown in Table I. Our own results are shown in Tables II, III. The findings are noteworthy in two respects.

Table I

Analysis of Cerebrospinal and Labyrinthine Fluids of the Cat and Guinea-pig: Results of Previous Investigations

Animal	Properties and constituents	Cerebro-spinal fluid	Perilymph	Endolymph	Reference
Cat	Osmotic pressure (g.NaCl/100g.H_2O)	1·017	1·046	1·058	Aldred *et al.* (1940)
	Index of refraction $\left(n_D^{22°C}\right)$	1·33435	1·33495	1·33455	Ledoux (1941)
	pH	7·45	7·87	7·82	Ledoux (1943)
	Chloride (mEq./l)	152	158	151	Ledoux (1950)
	CO_2(vol./100 ml. s.t.p.)	43·2	32·0	31·5	
	Protein (mg./100 g.)	31	268	118	
Guinea-pig	Sodium (mEq./l)	152	150	16	Smith *et al.* (1954)
	Potassium (mEq./l)	4·2	4·8	144	
	Chloride (mEq./l)	122	121·5	107	

Table II

Analysis of Serum, Cerebrospinal and Labyrinthine Fluids of the Guinea-pig and Cat: Results of Present Investigations

A. Guinea-pig

Constituent	Serum	Cerebro-spinal fluid	Perilymph	Utricular endolymph
Sodium (mEq./l.)	140 (4)	150 (12)	148 (12)	26 (8)
Potassium (mEq.l.)	4·5 (4)	4·0 (12)	5·0 (12)	142·0 (9)
Chloride (mEq./l.)	—	122 (9)	120 (9)	110 (3)
Protein (mg./100 g.)	—	20 (6)	75 (6)	25 (6)
Non-protein nitrogen (mg./100 g.)	—	21 (6)	20 (6)	21·5 (6)

B. Cat

Constituent	Serum	Cerebro-spinal fluid	Perilymph	Cochlear endolymph
Sodium (mEq./l.)	155 (12)	162 (12)	164 (12)	66 (12)*
Potassium (mEq./l.)	6·7 (12)	5·9 (12)	6·0 (12)	117·0 (12)*
Chloride (mEq./l.)	—	150 (4)	150 (4)	—
Protein (mg./100 g.)	—	25 (5)	142 (5)	—
Non-protein nitrogen (mg./100 g.)	—	20 (5)	21 (5)	—

*In many of these samples the Na+ and K+ concentrations suggested contamination with perilymph. Three samples, however, showed the high values for K given in the table. The bracketed figure appended to each entry represents the total number of observations upon which it is based.

Table III

Analysis of Cerebrospinal and Labyrinthine Fluids of the Guinea-pig: Present Investigations

Constituent	Cerebro-spinal Fluid	Perilymph	Endolymph
Calcium (mEq./l.)	3·0 ± 0·2	3·0 ± 0·2	3·0 ± 0·2
Magnesium (mEq./l.)	2·0 ± 0·2	2·0 ± 0·2	0·9 ± 0·2
Hexosamine (mg./100 ml.)		5–8	5–8

(1) Utricular endolymph has a high potassium concentration and a low sodium concentration compared with perilymph or cerebrospinal fluid.

(2) The protein level in perilymph is higher than that of the other fluids. In other respects, however, the composition of the perilymph approximates closely to that of the C.S.F.

These results provide strong evidence of a wide difference between endolymph and perilymph. They indicate, too, that perilymph is mainly derived from cerebrospinal fluid.

As shown in Table III, we have found that the calcium content of endolymph in the guinea-pig was similar to that of cerebrospinal fluid and perilymph, having a value of

3·0 mEq./l. A magnesium content of 2·0 ± 0·2 mEq./l. was found for perilymph and cerebrospinal fluid, but 0·9 ± 0·2 eq./l. only in utricular endolymph. This is only half the value found in the other fluids. This result once again adds emphasis to the fact that utricular endolymph, at least of the guinea-pig, is very different from the perilymph.

In 1953, Jensen and Vilstrup isolated hyaluronic acid from the labyrinths of *Acanthias vulgaris*. By pooling the contents of 300 of their labyrinths, the largest known, these workers obtained very large quantities of endolymph. This was found to be viscous, possessing a relative viscosity of 24·24, with a hyaluronic acid content of 73 mg./100 ml. Accordingly, they attributed the high viscosity to the presence of this large amount of hyaluronic acid in its polymeric form. It was thought that if such high viscosity was also found for the endolymph of the higher vertebrates it would be an important factor in the rapid damping of the fluid movements in the semi-circular canals. Further, the dilatation of the endolymphatic sacs observed in patients suffering from Ménière's disease might well be an osmotic consequence of the depolymerization of hyaluronic acid. Our own examination of the perilymph and utricular endolymph of the guinea-pig have revealed a hexosamine content of 5–8 mg./100 ml. If all this had existed as hyaluronic acid the concentration of the acid in both fluids would only be 10–15 mg./100 ml. which is considerably less than the 73 mg./100 ml. found by Vilstrup using elasmobranchi. It does not seem likely that the viscosity of the mammalian endolymph is much higher than that of perilymph, or C.S.F., whilst its small hyaluronic acid content is not likely to provide any explanation of the endolymphatic distension found in Ménière's disease. In addition, the samples of perilymph and endolymph examined, as judged by their behaviour in a capillary tube, exhibited no significant degree of viscosity.

To summarize the results for Na^+, K^+, Ca^{++}, Mg^{++}: these confirm the very special nature of the endolymph. Whilst the high K^+ low Na^+ content is characteristic of intracellular fluid, the Mg^{++} content is not, being, in fact, slightly lower than that of extracellular fluid.

Otologists will naturally wish to know how the remarkable chemical characteristics of the endolymph will help in the understanding of the mechanism of Ménière's disease. With regard to its metabolic function, the significance of its unusual electrolyte pattern is far from clear. Moreover, it is difficult to reconcile the high potassium content of endolymph with the positive DC potential of the scala media demonstrated by Békésy (1952). Here the electrical polarity is the reverse of that found for muscle and nerve, in which a negative potential is associated with the side of the membrane having a high K concentration. It is, however, possible that this positive potential provides the basis of the electric triggering of the response to sound of the hair cells of Corti's organ.

Regarding the formation of endolymph, the stria vascularis may well play the part already attributed to it of secretory action. The maintenance, however, of constant ionic levels on either side of Reissner's membrane probably involves a biochemical mechanism known as "active transport". Here an accumulation of K^+ and extrusion of Na^+ takes place against concentration gradients. This may maintain a high K^+ level, without any difference in osmotic pressure on the two sides of Reissner's membrane.

This osmotic pressure is intimately coupled with water balance. The breakdown of this mechanism would probably tend to disturb this water balance with resulting distension of the endolymph system. It is hoped that further analytical work will bring us nearer to a fuller understanding of these mechanisms, and so to the rational treatment of Ménière's disease.

Acknowledgments

Our thanks are due to the Editor of the *British Medical Bulletin* (Citron *et al.*, 1956) for kind permission to reproduce Figs. 1 and 2, and Tables I and II.

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Section of Otology with Section of Laryngology

JOINT SUMMER MEETING HELD AT THE UNIVERSITY OF BRISTOL

OTOLOGICAL SESSION

Chairman—PHILIP J. JORY, D.S.O., F.R.C.S. (President of the Section of Otology)

June 27, 1957]

A DISCUSSION was held on **Plastic Surgery of the Middle Ear.** The following opening papers were read: **Myringoplasty,** by Mr. STUART MAWSON; **Plastic Middle Ear Operations with Particular Attention to the Cavum Minor Technique,** by Dr. NILS G. RICHTNER (Stockholm); **Some Problems of Tympanoplasty,** by Mr. P. H. BEALES.

Mr. F. MCGUCKIN, Mr. R. L. FLETT, Mr. GAVIN LIVINGSTONE, Mr. I. B. THORBURN, Mr. I. SIMSON HALL, Mr. E. G. COLLINS, Mr. W. S. MCKENZIE, Mr. J. F. O. MITCHELL, Mr. E. H. RAINER and Mr. S. W. ALLINSON took part in the subsequent discussion.

LARYNGOLOGICAL SESSION

Chairman—J. ANGELL JAMES, M.D., M.R.C.P., F.R.C.S. (President of the Section of Laryngology)

[*June* 28, 1957]

A PAPER on **The Histochemistry of the Nasal Respiratory Mucosa** was read by Dr. MILES TAYLOR and was discussed by Dr. A. YOUNG, Professor F. C. ORMEROD and Mr. A. MACKENZIE ROSS.

Professor J. M. YOFFEY, read a paper entitled **The Passage of Fluid and Other Substances through the Nasal Mucosa,** which was illustrated by a film; it was discussed by Mr. R. G. MACBETH.

A Discussion on **Management of Post-cricoid Carcinoma** was opened by Professor F. C. ORMEROD, Mr. RONALD W. RAVEN and Dr. M. LEDERMAN. Dr. R. C. TUDWAY, Dr. SYDNEY CURWEN, Mr. H. D. FAIRMAN, Mr. I. SIMSON HALL, Mr. R. G. MACBETH, Mr. A. J. MOFFETT, Mr. R. D. OWEN, Mr. KENNETH G. MALCOMSON, Mr. GEORGE SEDD, Mr. R. S. LEWIS and Mr. J. A. SEYMOUR-JONES took part in the subsequent discussion.

[*June* 29, 1957]

A CLINICAL MEETING, arranged by the South Western Laryngological Association, was held at the Bristol General Hospital. A film on **Submucous Resection and Rhinoplasty** was shown by Dr. BEN WITHERS (Houston, Texas).

These meetings will be reported in the *Journal of Laryngology.*

BOOK REVIEWS

The Essentials of Modern Surgery. Edited by R. M. Handfield-Jones, M.C., M.S., F.R.C.S., and Sir Arthur E. Porritt, K.C.M.G., C.B.E., M.A., M.Ch., F.R.C.S. 5th edition. (Pp. xv+1276; illustrated. 75s.) Edinburgh and London: E. & S. Livingstone Ltd. 1957.

The greatest compliment which can be paid to a textbook is that it should be bought by successive generations of students and that further editions should be demanded from time to time. It is eighteen years since your reviewer was first sent a copy of this book and this is the fifth edition; an eloquent tribute to the excellence of the work.

This textbook is the result of multiple authorship and the editors have not put their contributors in strait jackets, but rather left them to go their several ways. The result is surprisingly homogeneous, but it has the advantage of presenting the work in a variety of styles which tends rather to hold the interest. The actual arrangement also has some unusual features. For example, the appendix still has a whole chapter to itself and this is quite right since diseases of this organ form such a large part of surgical practice. This particular chapter, written by Julian Taylor, still remains one of the most outstanding in the book. There is an excellent account of venereal disease, which is a subject rather neglected in modern textbooks. On the whole there is a nice balance held between the various sections of the book.

Criticism, which is only about details, arises chiefly because of over-simplification in some parts which is due to a laudable desire to keep the text as brief as possible. For example, it is not generally held that Dercum's disease is a manifestation of hypothyroidism. Seminoma is not separated from teratoma in the prognosis of tumours of the testicle; there is no mention of the stripping operation for varicose veins; subacute thyroiditis is not usually accompanied by a raised polymorphonuclear cell count; surely thiouracil is not still on trial and finally the description of the treatment of Hirschsprung's disease by removing the affected colon is rather ambiguous.

However, such points as the above are only minor criticisms of what is an excellent text to be put in the undergraduate's hands for learning his surgery. He would be well advised to keep it on his shelves for reference after qualifying. The printing is excellent and the paper of such good quality that the book is a little heavy for the binding in which it is produced. The illustrations are well chosen, numerous and of high quality. The whole format of the book is most attractive and Messrs. Livingstone have designed a cover which is in keeping with a number of their more recent publications.

A Text-Book of Psychiatry for Students and Practitioners. By Sir David Henderson, M.D.Edin., F.R.F.P.S.Glas., F.R.C.P.Ed. and Lond., and the late R. D. Gillespie with the assistance of Ivor R. C. Batchelor, M.B., F.R.C.P.Ed., D.P.M. 8th edit. (Pp. xii +746. 35s.) London, New York, Toronto: Oxford University Press. 1956.

Those who, like your reviewer, first read Henderson and Gillespie at a time when there was no comparable English work to challenge it, can only receive this the eighth edition with affection and pleasure. With this edition Sir David Henderson has a new collaborator in Dr. Ivor R. C. Batchelor who, in addition to other contributions, has rewritten the chapter on epilepsy which is now helpful and up to date. The sections on ætiology and on physical treatment have also been revised and rearranged.

Paranoid schizophrenia and paraphrenia have been discarded, and "paranoid state" has come to replace them, mainly on the grounds that paranoid states develop later, are not usually associated with deterioration, and—less acceptably—"have a strong affective component—which may be responsive to treatment". While the authors believe this simplification long overdue, it is doubtful whether everyone will regard it as helpful. Both paranoid schizophrenia and paraphrenia are well known and easily recognized entities and psychiatrists will probably continue to use these names in referring to them. It is useful to stress that paranoid symptoms can colour *any* psychosis including schizophrenia but the abolition of two diseases is perhaps a little drastic as a method of doing so.

By leaving much of a well-written book unaltered over a considerable period of time, the psychoses can be seen in their historical setting, and the psychoanalytic view of psychopathology is still set out in detail. While this at the best has an old-world look, and at the worst seems frankly bizarre, it is still desirable for the cultivated psychiatrist to know what McCurdy thought in 1925, not least perhaps because undergraduate medical students sometimes come to their hospital work fairly well informed on such matters.

If one criticism may be ventured, it is that the legal section should be revised—drastically. Here old-world phraseology cannot be excused on any grounds. Thus (page 683) there are

no longer any paupers or lunatics at large in this country. This is not so much due to redistribution of income as to the fact that Parliament abolished them in section 20 of the Mental Treatment Act of 1930. It should be noted too (page 683) that the Reception Order on Petition applies to non-private as well as private patients since the National Health Service Act of 1946.

These are small criticisms in a large work which can be cordially recommended as upholding the great tradition of its predecessors.

Psychosynthesis. A "Project for a Scientific Psychology". By John Pardey Crawford, M.D.Lond., M.R.C.P.Lond., D.P.M.Lond. (Pp. 104; 2 illustrations. 21s.) London: Ash & Co. Ltd. 1956.

This is a most interesting little book intended, it seems, to place related physical and psychological phenomena into relation with one another to form a "Gestalt" or integrated whole. In considerable measure Dr. Crawford has succeeded, and where he has failed it is because of the limitations of our knowledge and the inherent difficulty of the subject matter. The author's knowledge of the literature is extensive and the references are here available though not readily, for although they are listed at the end of the book, there is no index.

The survey is wide and must inevitably be greatly condensed in 92 pages, so that it is not an easy book to read. Providing the reader knows his individual trees—and there are many of them, then this book will show him the wood. Perhaps it would be fair to say that the book will be a joy to senior registrars especially in psychiatry, but will present difficulties to senior consultants both in psychiatry and neurology. Nevertheless, there are few who will fail to profit in some measure by reading it, and the book deserves to be successful. Some expansion in a future edition would make it easier for his readers to share the fruitful holistic standpoint of the author.

Anatomie Chirurgicale des Hernies de l'Aine. By Henri Fruchaud. (Pp. 488; illustrated.) Paris: G. Doin & Cie. 1956.

Le Traitement Chirurgical des Hernies de l'Aine chez l'Adulte. By Henri Fruchaud. (Pp. 386; illustrated.) Paris: G. Doin & Cie. 1956.

Henri Fruchaud was displaced from his surgical chair at the School of Medicine of Angers by Hitler's invasion of France. He served as surgeon to the Free French forces in the Mediterranean theatre of war, and at its close was appointed surgeon to the hospital of Saint-Louis at Aleppo. These two books deal with herniæ of the groin, a group that includes oblique and direct inguinal hernia, femoral hernia, and pre-vascular hernia (Nareth's hernia.)

Both volumes are encyclopædic in their completeness, and unique among books dealing with hernia in the number and technical excellence of their illustrations. These illustrations are so numerous and so beautiful that any reader, even though his knowledge of French gets no farther than "la plume de ma tante" stage, can follow them and learn from them. The volume on surgical anatomy starts with a chapter on the history of inguinal anatomy, introducing drawings by the ancient anatomists from Leonardo da Vinci to Astley Cooper, and concludes with one on the comparative anatomy of the groin in the anthropoids and in quadrupeds. The greater part is taken up with a detailed description of every structure in the inguinal region, illustrated by figures that in their accuracy of detail and their beauty of craftsmanship could hardly be excelled. The many variations in these structures, in the arrangement of the external oblique aponeurosis and the inguinal ligament, in the origins of the lower fibres of the internal oblique and transversalis, in the composition and insertion of the conjoined tendon, and the great variability in the strength and attachment of the transversalis fascia, are described and illustrated.

The second volume is equally well-produced. Dr. Fruchaud describes the well-known standard operations for the repair of hernia, and their modifications. Considerable space is devoted to the operation of repair performed at Aleppo, one that deals with the inguinal canal with a combination of French delicacy and Oriental ruthlessness. One can imagine the Professor, as he washes up for a hernia operation at Aleppo, saying to his Syrian House Surgeon:

> "Ah love! Could thou and I with fate conspire
> To grasp this sorry scheme of things entire:
> Would we not shatter it to bits,—and then
> Remould it nearer to the heart's desire."

Then he puts on his gloves and proceeds to do exactly that, to the astonishment and alarm of the English reader.

These two volumes are admirably produced, and they will remain standard works of reference on the surgery, and still more on the anatomy, of the inguinal region.

Section of Pædiatrics

President—D. V. HUBBLE, M.D., F.R.C.P.

[*February* 22, 1957]

MEETING AT QUEEN CHARLOTTE'S MATERNITY HOSPITAL, LONDON

DEMONSTRATIONS

I.—**Radiological Exhibit** by E. ROHAN WILLIAMS, F.R.C.P., F.F.R., and Miss A. E. MADDEN, M.S.R., on **Radiology in Respiratory Distress in the Newborn Infant.**

Approximately 80 neonatal chest radiographs were shown illustrating the following conditions:

(1) Anectasis (primary atelectasis).
(2) Hyaline membranes with secondary atelectasis (both with recovery and proven at post mortem).
(3) Migrating atelectasis.
(4) Liquor and meconium aspiration pneumonia.
(5) Intrapulmonary hæmorrhage.
(6) Staphylococcal pneumonia and abscess formation.

II.—**Human Milk Bureau:** Sister RIGGALL discussed details of the work carried out.

III.—**Pathological:** To show the normal bacterial flora of the umbilical cord and how it is affected by various applications, by R. M. CALMAN, M.B., Ch.B., and the clinical staff.

IV.—**Social Service:** Socially and physically unacceptable babies born in and out of wedlock were discussed by Miss NOBLE, A.M.I.A. (Head Almoner), and Miss GROOMBRIDGE, A.M.I.A.

V.—**Breast Feeding:** Investigation to show the value of special ante-natal and post-natal supervision. By Sister FAREBROTHER.

VI.—**Morbid Anatomy:** Causes of neonatal death with special reference to the respiratory system; development of neonatal lung; atelectasis and hyaline membrane formation in the neonatal lung and in the experimental animal; and demonstration of naked eye and histological specimens of various pathological conditions affecting the neonatal lung. By A. E. CLAIREAUX, F.R.C.P.

CLINICAL DEMONSTRATION

Cases 1–6 are cases with jaundice as a feature. In none were Rhesus antibodies concerned. Two were given exchange transfusions because the hyperbilirubinæmia seemed to be approaching a level likely to produce kernicterus.

I. Galactosæmia with Hyperbilirubinæmia Treated by Exchange Transfusion.—Dr. A. P. NORMAN.

Patricia K. (A.19411), female.

Born 21.6.55, a spontaneous vertex delivery at 39 weeks. Weighing 5 lb. 12¾ oz. she made good general progress until the age of 6 days when she became lethargic and refused all feeds. Jaundice, first noticed on the third day, had become marked (serum bilirubin 19 mg.%), the liver was enlarged one fingerbreadth and firm. At 8 days her condition remained poor with frequent vomiting. Galactose was demonstrated in the urine and feeds were changed to Galactomin. (Galactomin (1955) contained a proportion of lactose and is not the same preparation now marketed under this name.)

The baby's condition did not improve, the jaundice increased and an exchange transfusion of 450 c.cm. blood was given. Liver function tests showed thymol turbidity 1 unit, alkaline phosphatase 10 units, pseudocholinesterase 30 units (normally over 70 units).

Following transfusion the jaundice decreased. The baby's further progress was complicated by oral thrush at 11 days, a urinary infection at 25 days and several further febrile upsets for which no clear reason could be found.

At 62 days a galactose tolerance test (2·6 grams given) gave an abnormal result. Plasma electrophoresis (Dr. C. Forsyth) showed agammaglobulinæmia and following this two injections of gammaglobulin were given at weekly intervals. As progress was slow a special feed of groats, sugar and egg was tried. This was followed by vomiting and pyrexia and at 69 days feeds were changed to glucose and Hartman's solution. Chest X-ray showed a right mid-zone opacity.

Real progress began on the same solution with the addition of groats and sugar from the 87th day and the diet was gradually enlarged with liver and vegetables in the routine way. The baby was discharged at 102 days, clinically well, with a slightly enlarged liver, weight 8 lb.

At 4½ months, weight 10 lb. 11½ oz., she was doing really well. Further progress is reported as satisfactory, but she is thought to be somewhat slow in development at 20 months.

Family history.—The mother has had three previous pregnancies: The first child (1949) is now alive and well; the second (1950) weighing 5 lb. 9 oz. died with jaundice at 4 weeks and the third (1952) weighing 5 lb. 8 oz. died with jaundice at 6 weeks. *Sections of the liver* of one of these (Dr. M. Bodian): There is diffuse fine portal fibrosis with proliferation of portal bile ducts and dilatation of intralobular bile ducts, many containing bile. The ducts are lined by cuboidal epithelium, a change which has been noted in cases of "metabolic hepatitis," including galactosæmia.

II. Galactosæmia.—Dr. A. WHITE FRANKLIN and Dr. ISOBEL SMITH.

Baby L. (A.24111), female, was born 13.12.56, at term, weight 8 lb. 1 oz., length 20½ in. Pregnancy and delivery were normal, and condition after birth satisfactory. Feeding was difficult, thought to be due to the mother's very small nipples and large breasts.

The baby lost 8 oz. in four days and gained on the fifth day. Thereafter breast feeds were taken reluctantly, the baby was feeble and uninterested and weight dropped steeply to 7 lb. on the seventh day. The liver was slightly enlarged. On the eleventh day weight was stationary, tube feeding was started, slight jaundice developed and examination showed a large firm liver. On the twelfth day the condition remained poor, jaundice was more marked, liver firm and extended to umbilicus. Urine: Benedict's reaction positive, "Tes-tape" glucose test negative, methylamine test for lactose negative. Chromatography demonstrated a considerable amount of galactose. Blood: Group A, Rh positive, Coombs negative; total bile pigments 7·9 mg.% (direct 4·5 mg.).

Family history.—Mother weighs 20 stones, and comes of a very obese family. (Antenatal W.R. negative.) Father alive and well, as are the two previous children, born 1953 (weight 9 lb. 1 oz.) and 1955 (weight 7 lb. 6 oz.) both having been successfully breast fed.

Progress.—Improvement in feeding followed Galactomin, weight curve rose and at 4 weeks she weighed 8 lb. 2 oz. The liver was smaller. There has been no ophthalmic abnormality. A breast abscess developed which responded to oral Terramycin and drainage (*Staph. aureus*). At 7 weeks weight 8 lb. 12 oz. The liver was just palpable, and progress was normal on Galactomin feeding. One week later she started to cough, and oral thrush was noted. Despite treatment her condition deteriorated and she was admitted to St. Bartholomew's Hospital, aged 8 weeks, with thrush in the mouth and on the buttocks, conjunctivitis and acute respiratory infection; weight 8 lb. 15 oz. Urine contained no reducing substance but some excess of amino acids. Plasma electrophoresis

showed almost absent gamma globulin. Galactomin feeding was continued and there was some improvement, despite vomiting of large tough curds. However, a change to lactose-free synthetic "milk" mixture was followed by a gain of 1 lb. in one week with no further vomiting.

Family study.—Galactose tolerance curves of both parents are normal.

III. **Galactosæmia.**—Dr. A. WHITE FRANKLIN.

Susan D. (19.1.57), female, was born at full-term by spontaneous vertex delivery; weight 6 lb. 2 oz. She was breast fed but owing to the mother's sore nipples was fed expressed breast milk after two days. Weight dropped to 5 lb. 11 oz. on the third day and began to rise, reaching 5 lb. 12 oz. on the fifth day. During the next two days the baby began to refuse feeds and to lose weight again.

At 8 days she became jaundiced and lethargic, vomiting feeds; she commenced oral Terramycin as a case of possible infection. After improving on the 9th day, she deteriorated with more marked jaundice, vomiting food and a trace of blood. She was transferred at 10 days to St. Bartholomew's Hospital where she appeared jaundiced, ill, with a liver enlarged to the umbilicus and firm. Weight 5 lb. 4 oz. Blood: Hb 146%. Coombs negative, thymol turbidity 4·5 units, serum alkaline phosphatase 48 K-A units, serum bilirubin 5·9 mg.% (direct positive), pseudocholinesterase 37 units, W.R. negative. Urine contains galactose 5 g.% and excess of amino acids both in amount and number.

On the 13th day she commenced Galactomin with a weight gain two days later, reduction in size and firmness of liver, disappearance of galactose and excess amino acids from the urine. At three weeks there were improved liver function tests, thymol turbidity 1 unit, serum alkaline phosphatase 17 K-A units, serum bilirubin 0·4 mg.%: but the pseudocholinesterase level remained abnormal at 46 units.

On the 26th day she collapsed acutely ill, with refusal of all feeds, diarrhœa and vomiting, weight 5 lb. 14 oz. It was then appreciated that as well as lactose in small amounts in Galactomin, she had for seven days been taking one ascorbic acid tablet daily containing 65 mg. of lactose. A transfusion of 90 c.c. of fresh blood was given by drip hoping to introduce by this means the missing transferase; a course of tetracycline was started and one injection given of gammaglobulin, which had been noted as present but decreased in the baby's serum. She then began the special lactose-free diet with extra calcium as gluconate (0·45 gram in each feed) and Abidec 0·6 c.c. daily, to provide routine vitamins and any special vitamin B needed because of the absence of lactose and galactose from the diet. Weight gain and general progress have been excellent on this new regimen. Weight at 5 weeks 6 lb. 12 oz.

Family study.—Mother has a normal galactose tolerance curve. Father has a galactose index of 299 (normal range 0–160).

Discussion (Cases 1, 2 and 3):

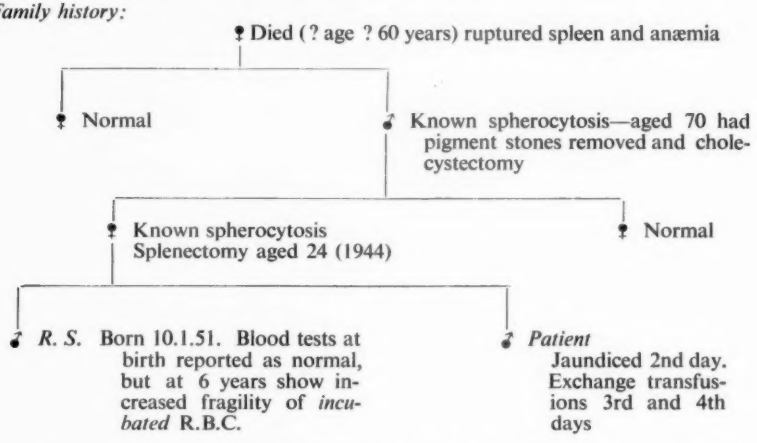
The three cases of galactosæmia come respectively from Weymouth, London and Welwyn Garden City. The first was expected owing to the death of 2 out of 3 siblings from liver disease at 4 and 6 weeks of age. In all progress was normal until the sixth day, from which time loss of appetite and loss of weight were followed by enlargement of the liver and jaundice. Pseudocholinesterase levels in 2 and 3 were low and the first 2 cases where there was a tendency to rather frequent infection have hypogammaglobulinæmia which may be physiological. All responded to diminished lactose feeding, although case 1 was very slow to gain. In Cases 2 and 3 the progress on modern Galactomin was not maintained and there was much vomiting of large tough curds. Both are now on a special lactose-free mixture made of egg, cereal, arachis oil fortified with calcium gluconate and extra vitamin B.

IV. **Congenital Familial Spherocytosis with Neonatal Hyperbilirubinaemia Treated by Exchange Transfusion.**—Dr. I. SMITH and Dr. A. WHITE FRANKLIN.

Philip S. (A.22384), male. Born 18.10.56, weighing 7 lb. 1 oz., by spontaneous vertex delivery, after 38 weeks normal pregnancy. Mother is Rhesus negative, without antibodies. Condition at birth was normal, without jaundice, anæmia or splenomegaly. Blood Group A, Rhesus positive, Coombs negative. Jaundice, first noted on second day, increased and became severe by the fourth day. Total pigment was 16·8 mg.% at 36 hours and rose at 60 hours to 26·4 mg. (direct only 1·0 mg.). At this time Hb 115% (fœtal Hb 66%); red cell fragility markedly increased, commenced at 0·52% and complete at 0·4%.

saline; spherocytosis marked. The increasing hyperbilirubinæmia led to exchange transfusion at 65 hours. (550 c.c. given and 560 c.c. removed.) Although at the end total pigment had fallen to 13·7 mg., eighteen hours later it had risen to 23·8 mg. (direct 1·3 mg.). A second exchange transfusion was given (570 c.c. given, and 555 c.c. removed). Thereafter jaundice gradually faded and he was discharged home on the 13th day, weighing 7 lb. 3 oz., Hb 103%. The spleen was palpably enlarged.

Family history:



NOTE.—All affected members of this family have been noticeably fair: auburn-haired. All unaffected members dark-haired.

Progress.—Since discharge progress has been excellent and at 4 months he weighs 15 lb. Spleen tip palpable.

Case shows *anticipation* in a family affected by congenital spherocytosis with a risk of kernicterus in what is assumed to be the fourth generation. Following the exchange transfusions the red cell fragilities returned to normal. On the 112th day increased fragility was clearly established again (Dr. H. F. Brewer).

V.—Congenital Extra-hepatic Biliary Obstruction, Bile Peritonitis, Choledocho-duodenostomy.—Dr. A. WHITE FRANKLIN and Mr. R. S. CORBETT.

Carol G. (S.B.H. 353078), female, born 22.8.56, weighing 6 lb. 12 oz. Pregnancy and delivery normal.

Meconium was passed on the third day and normal curdy stools were reported thereafter. She had a poor appetite, vomited occasionally and failed to gain weight. On the 24th day she was transferred to hospital for observation. The stools were noticed to be formed and white (Fouchet's test negative). There was no jaundice, no enlargement of liver or spleen. As there was no progress and jaundice appeared on the 34th day she was transferred to St. Bartholomew's Hospital, aged 35 days. The abdomen was somewhat distended, shifting dullness was noted, liver and spleen were still not enlarged.

Bilirubin 2·5 mg% direct negative: pseudocholinesterase 60 units (Dr. H. Lehmann). During the next ten days the abdomen increased in girth. Paracentesis produced 150 c.c. of heavily bile-stained fluid. Six days later, aged 7 weeks, the baby collapsed, respirations were laboured, pulse 170. After restorative measures Mr. R. S. Corbett explored the abdomen removing much bile-stained ascitic fluid and fibrin clots. The liver appeared normal and not enlarged. A large bile-containing cavity was found under the right lobe. What was assumed to be a cyst of the bile duct was anastomosed to the duodenum.

The baby made excellent post-operative progress and after two days passed brownish stools. Stools are at times white but Fouchet's test is positive. Clinical progress has been slow but sure. Liver function tests before operation were normal, except for pseudocholinesterase, which has risen to normal since (107 units at 3½ months).

Liver biopsy section (Dr. A. G. Stansfield) showed evidence of obstruction, with gross distension of sinusoids, and no disorganization of liver architecture. Bile pigment is present in many of the Kupffer cells and there are bile thrombi in the dilated canaliculi. Glisson's capsule is thickened with some organizing exudate on the serous surface.

VI. **Intra-hepatic Calcification, Staphylococcal Liver Abscess, following ? Occult Umbilical Sepsis.**—Dr. A. WHITE FRANKLIN.

Peter F., born 22.1.54 at 41 weeks, by spontaneous vertex delivery, weighing 9 lb. 10 oz. He was breast fed for five days and then weaned to bottle. At six days temperature rose to 101° F. Thrush was present and some signs suggestive of pneumonia. He improved with Aureomycin and was discharged from Queen Charlotte's Hospital, aged 25 days, well and completely normal on physical examination. After five days he became jaundiced and was admitted to St. Bartholomew's Hospital with rapidly increasing abdominal distension due to gross liver enlargement and splenomegaly. X-ray showed intrahepatic calcification, lungs were normal.

He ran a course of intermittent febrile attacks controlled to a limited extent by oral Terramycin, and failed to make real progress until aged 3 months. A diagnosis of portal pylephlebitis, probably secondary to occult umbilical sepsis, was made but no action taken and he went home aged 5 months weighing 13 lb. He became ill again at 10 months and eventually developed a sinus from the umbilicus from which bile and pus containing *Staph. pyogenes* were discharged. At 13 months a laparotomy (Mr. J. P. Hosford) revealed a thick-walled track from the umbilicus to an abscess cavity containing bile-stained pus between the lobes of the liver. He slowly recovered after drainage and has since made excellent progress. The calcification has been shown to be intrahepatic by tomography and remains visible at 3 years of age.

The Place of the Pædiatrician in the Maternity Hospital

By ALFRED WHITE FRANKLIN, M.B., F.R.C.P.

FIFTEEN years ago when this Section visited Cell Barnes Hospital, St. Albans, I read a paper on the place of the pædiatrician in the Emergency Medical Service. Among his functions was the supervision of newborn babies in Sector hospitals and evacuated maternity homes. Since those days the National Health Service has disseminated widely through the country physicians informed about the newborn. This same period has seen the recognition by almost all concerned of the logic of allowing, or even encouraging, these pædiatricians to take part in the care of the newborn. Because evolution is always a painful process, there have been problems and difficulties not yet all overcome. Similar problems have in the past surrounded the evolution of obstetrics out of midwifery, which in England has, so far, taken over 300 years.

It was the Chamberlen family and especially Dr. Peter, the elder, by his invention of the fenestrated forceps at the turn of the sixteenth to seventeenth centuries, who really brought the man-midwife seriously into obstetrics by way of the abnormal case. The Chamberlens were on the side of the midwives or at least of good midwives and on several occasions during the seventeeth century attempted to incorporate and make a society of midwives against successful official professional opposition.

In the course of time the man-midwife or midman has displaced the midwife to an assistant position. The midwife had always had responsiblity for the care of the newborn. Did the man-midwife displace her in this? If he did, it was subluxation rather than dislocation. Many obstetricians became knowledgeable about newborn babies and included sections on their care in health and disease in books and pamphlets. Pædiatrics owes much to these pioneers. Sir James Y. Simpson pleaded one hundred years ago for autopsies in all cases of neonatal deaths—a plea only now beginning to be answered.

This recent dawn of pædiatrics has drawn in the pædiatrician, first for the abnormal or sick baby. Here he was displacing both midman and midwife, a displacement not always easy and never complete. Now the pædiatrician is invited to concern himself with the whole problem of the newborn, normal and abnormal; but, it must be stressed that everything depends on the condition of the baby when the obstetrician hands it over.

One result of the change, making progress possible, has been to clear the doctor's mind of all concepts of disease and treatment, based on studies of the mature human. The child is not the human in little, nor the baby the little child. The neonate in its anatomy, its physiology, its pathology is a peculiar person. The metabolism of bilirubin in the newborn provides one clear example, as does the anatomy of the developing lung in prematures and many of the special histological changes.

I have purposely taken the title "the place of the pædiatrician", rather than "the place of pædiatrics", because pædiatrics has been practised in association with midwifery from the

earliest times. Someone has been at hand to tie the cord, to resuscitate the infant, to help decide whether to expose the abnormal infant on the nearest mountain top and—I suspect—to dogmatize about feeding. What is new is the idea that a specialist in diseases of children might be the best person to advise on the management of the newborn and on the treatment of disorder and disease during the mother's puerperium. Queen Charlotte's Hospital was founded in 1739. In 1929, after 190 years, Dr. Eric Pritchard was appointed its first pædiatrician, followed from 1936–50 by Professor Alan Moncrieff. These men and their successors took charge of pædiatrics but they did not take charge of all babies from the moment of birth. The obstetrician and the obstetric staff must dominate any obstetric hospital or department. Their duty is to help the greatest possible number of women to produce normal babies with the smallest possible risk and to launch them back into family life, well, happy, able to enjoy the feeding of and the caring for their babies, in a word—satisfied. The duty of the pædiatric staff as of all the other ancillary staff is to help the obstetrician to discharge this whole duty.

At present at Queen Charlotte's Hospital the functions of the pædiatric staff are:

(1) To advise in consultation with Matron and the nursing staff on the routine care and management of the babies, no change being made without the obstetricians' approval.

(2) To help in resuscitation in the labour ward in conjunction with the obstetrician and the resident anæsthetist.

(3) To take charge of all sick babies, including those suffering from birth trauma, respiratory disorders or infection.

(4) To advise about the management of all cases of congenital abnormality either physical or mental or both.

(5) To admit to the special nursery under direct care all premature babies of birth-weight 3½ lb. or less, or over if presenting a difficulty.

(6) To examine all babies of unmarried mothers before discharge.

(7) To be closely concerned with the management of babies where blood incompatibility is suspected or known and of babies of diabetic mothers.

(8) To examine all babies born to mothers with previous unexplained fruitless pregnancy or congenitally diseased or defective babies, or after fœtal exposure to adverse influences such as rubella, vaccinia or heavy irradiation.

(9) To advise about feeding problems; here specially trained nursery staff are most useful.

(10) To conduct an infant welfare clinic in conjunction with local authorities[1] and a follow-up clinic for special cases, such as congenital heart disease or cerebral palsy following neonatal difficulty.

(11) To advise about antenatal problems.

(12) To teach the midwives and the residents.

(13) To keep records in such a way as to allow of clinical research into the progress of special groups of neonates.

(14) To initiate or participate in laboratory research into normal and abnormal conditions.

In these activities the pædiatrician works with all the other hospital services and comes in contact with the local authority service outside.

Perhaps the pædiatrician's main contribution to the philosophy of a maternity hospital comes from his absolute need, which he shares with the almoners' department, to view the baby in the context of the parents and family. Never for him can the mechanics of delivery outweigh the human factor.

The conduct of a case of hæmolytic disease gives a good illustration of the team at work, with the whole staff represented. The authority given to the obstetrician to try to time the delivery demands from him in return a sense of responsibility towards the rest of his team.

In an advertisement for a pædiatrician for newborn work certain qualities are necessary—tact and discretion, to be able to work in a team, great patience and humility. He ought to be a source of knowledge, and if he is, he ought to be a well rather than a fountain.

[1]In 1917 a Physician was appointed to an infant consulting centre, quite early in this field.

A Historical Note on Queen Charlotte's Maternity Hospital and its Pædiatricians

By L. E. TURNER, F.H.A.

RESEARCH into old records has shown that Queen Charlotte's Maternity Hospital originated in 1739 when Sir Richard Manningham founded a hospital in a seventeen-roomed house in Jermyn Street, known as The General Lying-In Hospital. Its name was changed in 1810, when Queen Charlotte became its Patron, to The Queen's Lying-In Hospital, and after her death the title of Queen Charlotte's Lying-In Hospital was assumed. A Royal Charter of Incorporation was granted in 1885 and when this was amended in 1924, the present name came into use.

The following extracts from the Minutes of meetings of the Committee of Management tell the story of the pædiatricians:

November 21, 1916: "The Sub-Committee reported that after conferring with the medical staff they recommended that an Infant Consultation Centre be established at the new out-patient department of the hospital and that a Physician be appointed to take charge of it, that the qualifications be the same as those for the Physician to the ante-natal department, that in the first place attendance be required on one afternoon weekly at 2.30 and that an honorarium be paid if necessary which may be from £30 to £50 per annum."

January 16, 1917: "A report was received from the visitors and medical staff on the appointment of a Physician to the Infant Consultation Centre. They had considered the applications for the post and unanimously recommended the appointment of Miss M. G. Thackrah."

Record of Attendances at the Infant Consultation Centre

1917 (9 months)	265	new patients—attendances were not recorded for these three years
1918	171	
1919	237	
1920	1,764	
1921	2,324	
1922	2,359	
1923	2,546	
1924	2,693	
1925	3,667	
1926	3,483	
1927	4,288	

Record of Attendances at the Infant Consultation Centre (contd.)

1928	4,546
1929	3,721
1930	3,964
1931	4,008
1932	4,493
1933	4,132
1934	4,291
1935	4,408
1936	2,949
1937	2,592
1938	2,465

The records for succeeding years are not available.

Dr. Thackrah resigned in 1931 and was succeeded by Dr. Gibbens, the Assistant Pædiatrician, who had been appointed to that office in 1930; thereafter the posts of Assistant Pædiatrician and Physician-in-Charge of the Infant Consultation Centre were combined.

November 18, 1929: "It was resolved that the proposal for the appointment of a Pædiatrician be approved and that the appointment be offered to Dr. Eric Pritchard. It was understood that Dr. Pritchard would be willing to accept the post for at least a year during which time he would organise the proposed department. It would be necessary to appoint an Assistant but it was decided to leave this to a later date."

NOTE.—Dr. John Hartley Gibbens was appointed Chief Assistant to the Pædiatrician in 1930. He resigned in 1933 whereupon Dr. Alan A. Moncrieff was appointed Assistant to the Pædiatrician with effect from May 1, 1933, succeeding Dr. E. Pritchard as Pædiatrician at the end of 1936 and resigning in November 1950.

Hæmolytic Disease of the Newborn

(I) **Serology.**—By JOHN MURRAY, M.D.

THE organization for the treatment of hæmolytic disease at Queen Charlotte's Hospital was discussed by *Dr. John Murray*, Director of the Bernhard Baron Research Laboratory. He said: At their first attendance blood is taken from all patients and tested for blood group Rh type and irregular antibodies. Rh-negative patients are retested for antibodies at

30 and 35 weeks. The finding of antibodies brings the patient into a special group with an additional separate system of notes and note filing. A wall chart, accessible to all staff, notes the expected date of delivery and all concerned are alerted when labour is expected or induced. This minimizes emergency arrangements and allows for the use of fresh blood for exchange transfusion. A consultant is in charge of the exchange, and has at least two other doctors in the hospital experienced in the method, together with some special members of nursing staff. The 24-hour pathological service enables bilirubin levels to be measured at 12-hourly intervals when necessary. Such arrangements are only possible with units dealing with a number of cases each year and probably 50 is the minimum for efficiency. The extra experience and skill of nurses and doctors in teaching hospitals counterbalance the usually small number of cases.

Control of bilirubin levels by exchange transfusion cuts down loss of life. In 1956 60 Rh-negative women with antibodies had 61 pregnancies. The 13 babies lost included 1 miscarriage, 3 abortions, 6 macerated hydropic stillbirths and 3 neonatal deaths. The present problem is to save intra-uterine loss by early induction at 35 or 36 weeks where it is expected that the baby will be seriously affected. Induction at 36 weeks should be considered when the mother has had a previous stillbirth or kernicteric or a baby requiring an exchange transfusion, or in any case where the antibody titre rises rapidly, even in a primigravida. Cæsarean section should be carried out at 32 weeks when the mother has had two intra-uterine deaths if the father is homozygous. Eight years' experience has shown only a 20% chance of survival when this type of case is allowed to go beyond 36 weeks. Efficient pædiatric treatment has lowered the neonatal death rate in prematures, especially of 4 lb. birth weight and over, and this is probably a normal weight for a healthy fœtus at 32 weeks.

If the baby is affected, the factors leading to the decision to exchange at birth are: a birth weight under 5½ lb., a cord blood Hb below 105%, a rise of bilirubin of 10 mg. per 100 ml. within twenty-four hours, and a history of previously badly affected infants. A repeat or late exchange is indicated when the bilirubin rises steeply and reaches or seems likely to reach 20 mg. per 100 ml., the levels being estimated twelve-hourly.

Early induction, which should be done by artificial rupture of the membranes, is only safe in units where bilirubin may be tested at regular intervals.

(2) Clinical Aspects of Exchange Transfusion.—By A. P. NORMAN, M.D., F.R.C.P.

MY intention is to describe briefly the technique of exchange transfusion used at Queen Charlotte's Hospital, to discuss the indications for secondary exchange, and to describe one case of special importance.

This hospital is fortunate in the interest which Dr. Murray and Dr. Lathe take in the problem of exchange transfusion, and the credit for our good results must go to them. My part is to co-ordinate and oversee the transfusion, although the exchange itself is usually carried out by the pædiatric resident, once the latter has the knack of doing it and has learnt our methods. These are more complicated because we gather information from individual samples of blood collected during the exchange.

We consider it important to use blood not more than twenty-four hours old. The blood is grouped and spun down, and plasma removed to give a hæmoglobin concentration of about 100%. We recommend that the blood be never heated, because of the risk of overheating, and we believe that it reaches an adequate temperature during preparation for the transfusion and during its passage along the tubing.

The baby is given oral digoxin, 0·125 mg. or 0·0625 mg. according to its weight, over or under 4½ lb., as soon as it is decided to carry out an exchange. We take a cord blood hæmoglobin of 105% as the critical level, but consider such other factors as the previous maternal history and antibody rise. Chloral 1 grain was given routinely until recently. The baby's legs are bandaged to a crucifix, the arms left free.

Blood is given in quantities of 10 c.c. at the rate of 10 c.c. per minute timed by a stop watch. In the hands of an expert 20 c.c. may be perfectly safe and I recently met a pædiatrician who completes his exchanges in thirty minutes by taking and giving 40 c.c. at a time. It would seem safer to transfer small rather than large amounts and 10 c.c. allows a good exchange. We aim at a total of 80 c.c. per pound. An advantage of a relatively slow and leisurely exchange is that time is given for the metabolism and excretion of possible harmful substances.

As a cause of death during transfusion, the laboratory staff suggested overloading of the heart and demonstrated gross errors in the estimates of blood given and removed, leading in general to overloading, though in one case to exsanguination.

Now, the blood is poured into a tall graduated container, against the level in which the estimated volume of blood given can be checked. The amount of blood removed is accurately weighed after each aspiration. The weighing machine used for this is an expensive instrument, but should be bought for big centres, while smaller ones could use a second tall measuring flask in which to put and measure the discarded blood. A cumulative error of 1–2 c.c. at each extraction of blood may reach a considerable size, so big that no one ever believes it until it is demonstrated.

We believe that because of careful attention to all points described, we no longer get deaths resulting from exchange transfusion, nor even real trouble. The use of the soft plastic catheter from Pharmaseal Laboratories, California, has made the operation both simpler and safer. This catheter is easy to insert and remains very comfortably in position without being held.

Apex beat rate and respiratory rate are recorded throughout the exchange by a *senior* nurse, who is responsible for reporting to the operator changes in the baby's condition. Formerly, we noticed that a slow rise in apex beat rate preceded the baby's collapse; not a sudden rise from crying, but a gradual increase of 20–30 beats per minute. The recording now is almost always flat, probably a beneficial effect due to the digitalisation. The venous (umbilical vein) pressure, always taken before the exchange begins, determines the size of the initial negative balance and the caution with which we proceed thereafter. There need be absolutely no urgency in the exchange and one should always stop and start again after a rest if the baby has appeared at all upset.

What is the critical level of bilirubin above which kernicterus may occur? First of all, in the best hands there is a potential error of 1–3 mg. in the estimate. Secondly, drugs, for example gantrisin, and perhaps other unknown changes such as physico-chemical differences in the baby, may lower the level of bilirubin at which cell damage occurs.

It is, therefore, unwise to dogmatize on the exact critical level. We know that kernicterus can occur with a level not much higher than 34 mg. per 100 ml.

Apart from one untreated case in a premature infant, we have had only one likely kernicterus in the past 3½ years. He is now aged 6 months, makes doubtful response to sounds and is backward in development. His case illustrates two points. Firstly, his known bilirubin did not rise above 29 mg., but his actual level may have been up to 32 mg. Secondly, the tragedy here was really the result of failure to check the bilirubin level until twenty-four hours after the exchange and of a further delay of about four and a half hours before doing the second exchange. This emphasizes the occasional need for urgency in starting these late exchanges and the necessity for an organization with sufficient personnel to carry out an exchange at any time and without delay.

Professor G. H. Lathe discussed the biochemical aspects of bilirubin metabolism as it affected the management and treatment of hæmolytic disease. His basic work has already been published elsewhere: BILLING, BARBARA H., COLE, P. G., and LATHE, G. H. (1954) *Brit. med. J.*, ii, 1263; (1957) *Biochem. J.*, **65**, 774. LATHE, G. H. (1954) *Biochem. Soc. Symposia*, **12**, 34; (1955*a*) *Brit. med. J.*, i, 192; (1955*b*) *Proc. R. Soc. Med.*, **48**, 271.

[*March* 22, 1957]

Sexual Precocity, Advanced Bone Age and Skin Pigmentation. ? McCune-Bruch-Albright Syndrome.—BRUNO GANS, M.D., M.R.C.P.

S. C., girl, aged 4½ years.

Family history negative.

Past history.—No neonatal jaundice, no exposure to œstrogens. Skin pigmentation first noticed in infancy. Normal development until the age of 3, when enlargement of the left breast was first noticed.

At 4½ her height, weight and mental development were normal for her age. Breast tissue was present on the left, but not on the right. There was a fine pubic down, but no proper pubic or axillary hair, and she had not menstruated. Rectal and abdominal examination was negative.

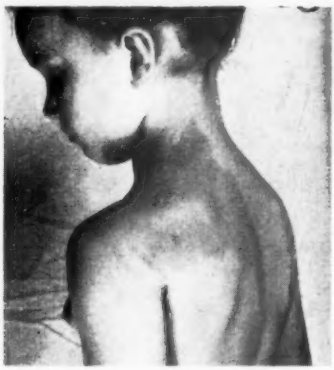


FIG. 1.—Aged 4½. Showing pigmented nævus and breast development.

A flat café-au-lait nævus was present over her left upper arm, her shoulder and her shoulder blade (Fig. 1).

A skeletal survey showed her bone to be at least two years in advance of her chronological age, this being a characteristic and constant finding in the syndrome. There was no evidence of polyostotic fibrous dysplasia. This type of osteitis fibrosa often does not make its appearance for several years after other features of the condition have been noted (Freedman, 1932; Peterman, 1956; Caffey, 1956).

17-ketosteroid excretion and F.S.H. production were normal. A vaginal smear stained by the Papanicolaou technique showed some pink squames, evidence of increased œstrogen production.

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Eosinophilic Leukæmia in Eosinophilic Family. ? Larva Migrans Syndrome.—A. A. CUNNINGHAM, M.D., M.R.C.P., and F. R. ELLIS, M.D.

J. W., girl, born 15.8.54. Birth weight 6 lb. 2 oz. Premature delivery at 36 weeks after uneventful pregnancy. No pre-natal radiological investigation of the mother. Normal birth. Admitted to hospital 5.11.56.

History.—Listlessness, general irritability, poor appetite and disturbed sleep for one month, dating from a cold in the head. For some time the child had been in the habit of eating earth, coal dust, etc. Seen by family doctor on 2.11.56 and sent for blood count: Hb 76%. R.B.C. 5,000,000. C.I. 0·76. W.B.C. 89,400 (polys. 6%, lymphos. 23%, large hyalines 1%, eosinos. 69%). Some "basket" cells present. Very occasional "t[illegible]k" cells. The R.B.C.s show slight achromia and marked anisocytosis. This points to a possible diagnosis of eosinophilic leukæmia but all other forms of eosinophilia should first be ruled out.

Family history.—Father and mother alive and well. Mother has had iron deficiency anæmia. First child stillborn at 5–6 months. Brother of 5 was treated for anæmia, now well: sister of 4 had pica which disappeared at 2½ years of age: sister of 9 months alive and well.

General examination (5.11.56).—Temperature 98° F., P. 112, R. 24. Child very irritable and obviously anæmic. One gland was particularly noticeable in the posterior triangle of the left neck. Throat showed tonsils of moderate size without exudate. *C.V.S.* normal. B.P. 88/60. R.S.—normal. Abdomen—Liver enlarged 3 fingerbreadths below costal margin. Spleen not palpable.

6.11.56: *Stool:* No red blood cells, mucus, pus, ova or parasites seen. *Urine:* Clean specimen: faint trace of albumin. Deposit: occasional pus cell. *Mantoux* 1/10 — Negative.

7.11.56: Marrow puncture: Leucoblasts 6·0%, promyelocytes 4·0%; myelos: neut[illegible].

2·0% *eosino.* 18·0%, baso. —; metamyelocytes: neutro. 4·0%, *eosino.* 8·0%, baso. 0·2%; polymorphs: neutro. 6·0%, *eosino.* 28·0%, baso. 0·2%; lymphos. 14·0%, monos. 0·4%, reticulum cells 0·2%, megakaryocytes 0·1%, plasma cells 0·4%, proerythroblasts 0·4%, normoblasts: polychromatic 5·0%, pyknotic 3·1%; myeloid—erythroid ratio 9·4 : 1. "The marrow picture is either that of eosinophilic leukæmia or an eosinophilic leukæmoid reaction. The former would appear to be the more likely diagnosis."

8.11.56: *Throat swab:* Heavy growth of *M. catarrhalis* and pneumococci.
X-ray of chest: No abnormality.
9.11.56: *Blood Wassermann reaction* negative.
9.11.56: *Blood count:* Hb 56%. R.B.C. 3,800,000. W.B.C. 30,000 (polys. 7%, lymphos. 19%, large hyalines 2%, eosinos. 72%). Platelets 200,000/c.mm. There are a few eosinophilic metamyelocytes, but most of the eosinophils are well formed. No nucleated reds seen.

Treatment.—Prednisolone 10 mg. 6-hourly (=40 mg. daily).
16.11.56: *X-ray of long bones and skull:* No abnormality of bone structure.

On admission the child could not feed herself, but now takes food satisfactorily and feeds herself very well. Her whole temperament has changed. On clinical examination, however, the liver is still enlarged. Spleen not palpable.

18.11.56: *Blood count:* Hb 52%. W.B.C. 8,000.
19.11.56: Progress maintained. B.P. 100/60. Prednisolone reduced to 15 mg. b.d.
20.11.56: *Repeat marrow puncture:* myeloblasts 5·6%, promyelos. 6·0%; myelos.: neutro. 14·4%, *eosino.* 1·4%, baso. —; metamyelocytes: neutro. 27·4%, *eosino.* 2·4%, baso. 0·2%; polymorphs: neutro. 15·0%, *eosino.* 1·4%, baso. 0·2%; lymphos. 16·0%, monos. 0·8%, reticulum cells 0·2%, megakaryocytes 0·2%, plasma cells 0·4%, proerythroblasts 0·4%, normoblasts: polychromatic 4·0%, pyknotic 4·0%; myeloid—erythroid ratio 8·8 : 1. The marrow picture is now completely different as the eosinophilic series have reverted to normal.

At this stage the possibility of *Toxocara canis* infection was discussed. Samples of stools from the dog and from the dust of the patient's home yard showed no ova or parasites of any kind.

21.11.56: Good progress maintained. Liver still enlarged, but smaller: 2–3 fingerbreadths below costal margin. B.P. 120/80.
23.11.56: *Blood count:* Hb 54%. W.B.C. 10,000 (polys. 70%, lymphos. 23%, large hyalines 4%, *eosinos.* 3%). Film: R.B.C.s show extreme hypochromia and moderate anisocytosis. No abnormal W.B.C.s were seen.
29.11.56: Prednisolone reduced to 10 mg. b.d.
3.12.56: Good progress maintained.

Blood count: Hb 56%. W.B.C. 10,000 (polys. 72%, lymphos. 21%, large hyalines 2%, eosinos. 5%).

Fæcal specimens from W. family: No ova or parasites seen, in any specimen from father, mother, two sisters or brother.

6.12.56: *Blood chemistry:* Serum proteins 7·2, albumin 6·2, globulin 1·0 grams %. Alkaline phosphatase 10 King-Armstrong units. Thymol turbidity 2·5 units. Bilirubin: total less than 0·5 mg.%. Serum phoresis: Emphasis of alpha globulins and mucoproteins and virtually absent gammaglobulin. Alpha lipoprotein increased and beta lipoproteins diminished. No biochemical evidence of hepatic dysfunction.
11.12.56: Good progress maintained. B.P. 124/78. Prednisolone reduced to 5 mg. b.d.
15.12.56: *Blood count:* Hb 56%. W.B.C. 10,000 (*eosinos.* 13%).
20.12.56: *Blood count:* Hb 64%. W.B.C. 8,000 (*eosinos.* 7%). E.S.R. 16 mm. in one hour (Westergren).
24.12.56: B.P. 110/70. Prednisolone reduced to 2 mg. t.d.s.
29.12.56: Liver slightly enlarged 1–2 fingerbreadths. Child discharged from hospital.
9.1.57: *Blood count:* Hb 92%. W.B.C. 18,000 (*eosinos.* 32%, basos. 1%). Film: R.B.C.s show slight anisocytosis.

General report.—Child very well. Liver one fingerbreadth below costal margin. No enlargement of spleen. Eating and sleeping well. Up and about.

16.1.57: Prednisolone reduced to 1 mg. t.d.s.
4.2.57: *Blood count:* Hb 89%. W.B.C. 24,000 (polys. 20%, monos. 3%, *eosinos.* 60%). Film: R.B.C.s show slight anisocytosis. Child full of energy. B.P. 120/80.
20.3.57: *Blood count:* Hb 90%. W.B.C. 25,000 (*eosinos.* 40%). Occasional eosinophilic metamyelocytes. No "blast" cells or nucleated red blood cells seen.
Child remains very well. Prednisolone 1 mg. t.d.s. continued.

All the near relatives of this child were carefully investigated with complete blood counts:

TABLE I

	Leucocytes	Eosinophils
Maternal grandfather ..	9,300	280
,, grandmother ..	5,600	112
Father	10,200	102
Mother	6,000	360
Mother's sister	6,000	360
Brother aged 5	10,000	1,600
Sister aged 4	9,000	2,200
Sister aged 9 months ..	11,000	1,320

DISCUSSION

Some hæmatologists are reluctant to recognize the existence of eosinophilic leukæmia owing to the difficulty of differentiating it from an eosinophil leukæmoid reaction. Space does not allow a detailed discussion on this point, but when all evidence is considered it would appear that eosinophilic leukæmia is a definite and distinct entity, although exact diagnosis during life or before the terminal phase may be extremely difficult. The latter statement applies equally well to some cases of neutrophilic and lymphatic leukæmia and is not a valid argument against the existence of eosinophilic leukæmia.

Eosinophilic leukæmia in childhood on a basis of strict diagnosis is exceedingly rare and less than 10 cases, predominantly male, have so far been reported.

The original blood picture and myelogram in this case could be that of an eosinophilic leukæmia or an eosinophil leukæmoid reaction. The marked anæmia abnormal electrophoretic pattern, increased E.S.R., enlarged liver and the absence of evidence to date of other conditions known to cause eosinophilia are in favour of a diagnosis of eosinophilic leukæmia.

The differential diagnosis of disorders characterized by extreme eosinophilia covers various infections, allergic conditions and parasitic infestations. The possibility of parasitic infestation is being carefully examined. This condition, which has been described by Heiner and Kevy (1956) under the heading "visceral larva migrans" is becoming better known, particularly in the U.S.A., but so far we have not seen any cases reported in this country.

The syndrome is caused by the ingestion of embryonated ova of the dog or cat roundworm (*Toxocara canis* or *Toxocara mystax*) and similar syndromes are caused by other parasites. The infestation is widely prevalent in young cats and dogs and larval infestation in man is probably more widespread than has been generally realized to date. Patients present with enlargement of the liver, perhaps also of the spleen, in association with leucocytosis and marked eosinophilia, the eosinophils making up to 80% of the total count. The laboratory aids to diagnosis are in the process of development, but hypergammaglobulinæmia has been noticed in some cases. Liver biopsy has shown the presence of eosinophilic granulomata. Examination of the dust from the neighbourhood of patients' homes has produced the toxocara ova. Various immunologic tests have been found of value. In this patient frequent examinations of the dust from the neighbourhood of her home have produced negative results. The fæces of the dog have also been examined with negative results. The child has not been in contact with any other domestic animal, and the absence of hypergammaglobulinæmia is against the diagnosis. Blood serum has been sent to Dr. D. C. Heiner, U.S.A. (*see postscript*).

In addition, repeated examination of the stools of the family has been made for other infestation, but there has been no evidence to date.

The investigation of the family also points to another rare condition, familial eosinophilia. Gray and Shaw (1949) reviewed 15 cases, including their own, but in some of the families an alternative diagnosis could be suspected. Without other causation after routine investigation, this family with the relatively high eosinophilic counts can reasonably be regarded as coming within this category.

CONCLUSION.—This case is presented as one of eosinophilic leukæmia with familial eosinophilia. The immediate response to prednisolone, both in the peripheral blood and in the marrow are of particular interest. Both the patient and family will be carefully followed up and details reported at a later date.

PS. (30.8.57).—Report from Dr. D. C. Heiner: After careful testing of the serum supplied, the results point to a considerable likelihood that the patient is suffering from the "visceral larva migrans syndrome."

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Diverticulum of the Heart. Ventricular Extension into the Abdominal Wall with Large Ventral Hernia.—PATRICIA WOOLF, M.B., B.Ch. (for R. H. DOBBS, M.D., F.R.C.P.).

M. B., female, aged 1 year. Admitted aged one day with a diagnosis of exomphalos.

On examination.—Weight 5 lb. 9 oz. Vigorous infant. Large ventral hernia with divarication of recti to just below umbilicus. Pulsating mass synchronous with apex beat, below xiphisternum, about 1 in. long, ½ in. wide, running slightly to right. Leading from its apex and running towards the umbilicus was a thin pulsating vessel lying superficially. No cyanosis. Respiration rapid 80–90, with some recession. Arterial pulsation in neck. Femoral pulses present. Blood pressure right arm 110/70. Heart enlarged, dullness to nipple line on both sides.

Screening (Dr. C. A. Neill): Heart centrally placed, markedly enlarged, apex probably on left. Vascularity increased.

Barium swallow: Left aortic arch.

ECG: Suggested dextroposition of heart. Balanced axis. Slight left ventricular preponderance. Record over diverticulum showed marked QRS complex, deeply inverted T-wave. The large complexes over the pulsatile swelling presented strong confirmatory evidence of myocardial diverticulum, not aberrant artery.

Progress.—Satisfactory except for some umbilical sepsis until aged 19 days, when shortly after strapping ventral hernia she developed pneumonia. Improved with digitalis and antibiotics. At this time she developed a blowing systolic murmer over lower præcordium.

Discharged at age of 1 month on Digoxin 0·025 mg. t.d.s. Progressed well and occasional mild upper respiratory infections resolved without antibiotic therapy.

Seen at 1 year. Weight 11 lb. 4 oz. No cyanosis, but generalized dusky skin colour. Dilated superficial veins over anterior chest. Præcordial systolic murmur, accentuated when supine. Pulmonary second sound accentuated and split. X-rays show progressive cardiac enlargement and the pulmonary circulation is now considerably increased. There is presumably a very large inter-auricular septal defect and possibly an interventricular septal defect.

Cardiac diverticula have been described communicating with the right and left ventricles. The majority communicate with the left ventricle, and are often associated with other lesions of the heart.

Skapinker (1951), reporting a case from Johannesburg, reviewed 12 cases, the earliest of which occurred in 1837. In this series only one survived infancy without surgical intervention and he died as a result of rupture of his diverticulum at the age of 4 years.

There appear to be two methods of dealing with this condition surgically; either by replacing the diverticulum into the pericardial sac and closing the opening in the diaphragm, or by resection of the diverticulum.

Snellen *et al.* (1952) reported another case from Holland, which was fully investigated during life, and in which the pericardial reflections were well demonstrated at autopsy. More recently Parsons (1957) described a further case and gave reasons for thinking that this anomaly arose during the ninth week of fœtal life.

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Huntington's Chorea.—R. C. ROXBURGH, M.D., M.R.C.P. (for C. T. POTTER, M.D., F.R.C.P.).

B. H., girl aged 11 years 4 months.

History.—November 1952 (aged 7): sudden onset of dysarthria; previously well. Three months later developed ataxia and nocturnal enuresis, followed by a tendency to jerk her head to the left. First seen nine months after the onset of symptoms, in August 195 . Then appeared to have normal intelligence, but there was a gross slurring dysarthria; ataxia not apparent. C.N.S. normal. Speech therapist found that the main speech defect was due to poor lip movement, and started treatment. However, there was no improvement at all. By February 1954 (aged 8 years, 3 months) dysarthria worse and gait more unsteady. Once again, no definite abnormalities could be detected in the C.N.S., apart from a variable ataxia when walking. C.S.F. normal. W.R. and Kahn negative. X-ray of skull normal. Mantoux negative.

Referred to Psychiatric Department. I.Q. found to be 86. Diagnosis of hysteria was considered.

By October 1955 (aged 9 years, 11 months) showing more deterioration with increased dysarthria, and inco-ordination. Now coarse choreiform movements of the head and face. Her mentality appeared unaffected.

A course of lysivane was given for twelve months (Oct. 1955 to 1956) with slight temporary improvement.

Past history.—Normal developmental milestones. No relevant illnesses.

Family history.—Father died 1953 (aged 44) in a mental hospital, from Huntington's chorea complicated by miliary tuberculosis and meningitis. Diagnosis made at St. Bartholomew's Hospital eighteen months before death, despite the completely negative family history. Mother alive and well. 2 male siblings of patient aged 19 and 15 alive and well.

Present condition.—Nervous apprehensive child, showing coarse choreiform movements of head and face. Jerks her head frequently. Coarse intention tremor in both arms, but can still write her name with a pencil. Speech is almost unintelligible and slurred. Mentality: understands everything said to her and responds normally. Can read simple books.

Psychiatric report (Dr. Bowley): I.Q. 71 (Wechsler scale). Performance indicates intelligence considerably below average. Very possibly there has been some deterioration since last test, which was 86.

C.N.S.—Cranial nerves normal. Sensation normal. Arms: Tone is slightly increased, all reflexes normal, co-ordination very poor. Coarse intention tremor. Legs: Tone increased. Reflexes equal and rather brisk. Plantar responses flexor. Co-ordination fair, but gross ataxia on walking. Romberg's tests negative.

Comment.—It was with some reluctance that a diagnosis of Huntington's chorea was made in this girl, in view of the rarity of the disorder in children and the absence of a definite family history, preceding her father. In fact, it is only in the past six months that we have seriously considered Huntington's chorea in her case. Previously, a hysterical or functional disorder had been considered possible and latterly, when progress was for the worse rather than for the better, an extrapyramidal degenerative disorder seemed to be developing.

However, in view of the reports received from the hospitals concerned with the father's illness which showed that classical Huntington's chorea had been diagnosed confidently, we felt that no other diagnosis was really possible in this girl. Indeed, the girl's mother has recently told us that she is developing just as her father did, and makes exactly similar movements.

Huntington's chorea, which is so very uncommon in childhood, is genetically a dominant disorder and usually 50% of children of an affected parent will develop the disease. There is no sex linkage. The onset of symptoms is gradual, the commonest age of onset being 35 years. Only 2% of cases began in childhood (Bell, 1934). Most commonly, dysarthria is the earliest presenting symptom, inevitably followed by coarse choreiform and jerking movements, together with a peculiar ataxia. Mental deterioration is always a late development and is the beginning of the end. Death occurs 10–15 years from the onset.

This remarkable disease is generally regarded as a rarity in this country, but recent papers by Pleydell (1954, 1955) and by Bickford and Ellison (1953) have shown that in country districts, at any rate, there are 5–6 cases at any one time per 100,000 of population, from which they calculate a possible 2,000 cases in England and Wales alone.

Most early papers on Huntington's chorea emanated from the U.S.A. You may remember the fascinating studies which showed a positive family history in a family in the Eastern States going back 300 years to a small village in Suffolk from whence some affected persons had emigrated to America in the seventeenth century (Davenport and Muncey, 1916). In the U.S.A. the incidence is remarkably similar to ours, namely 5 per 100,000 of population (Lazarte *et al.*, 1955).

It is generally regarded as a disorder especially likely to be found in isolated country areas and a recent paper by Bickford and Ellison (1953) showed a high incidence in Cornwall. It is also common in Suffolk, Norfolk, Northampton and Devon.

Several writers have noted that the victims of this disease show heightened sexual activity and large families are commonly encountered (Pleydell, 1954). This activity may be the result of very early cortical degeneration.

The prevention of this disorder is naturally extremely difficult since most families have been started before the affected parent shows symptoms. The only effective measure would be to prevent marriage of all children in an affected family.

There is no good evidence of the disease skipping out a generation and reappearing later.

In our case it is possible that miscegenation may have occurred, but we have no proof or evidence.

Some families appear to have started up from a mutation.

Treatment is highly unsatisfactory. Some recent reports from U.S.A. have suggested that reserpine may benefit the hyperkinesis for a time (Lazarte *et al.*, 1955).

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Neonatal Addison's Disease.—G. R. SPARROW, M.B., B.S., D.C.H. (for J. SAKULA, M.D., M.R.C.P., D.C.H.).

C. H., boy aged 3 months.

Past history.—Born 8.12.56 following normal pregnancy, labour and delivery. Birth weight 8 lb. 6 oz. First child.

Family history.—Healthy unrelated parents. No relevant history.

Progress.—Satisfactory, except for marked weight loss, until vomiting began on the eighth day, occasionally bile stained. Investigation for intestinal obstruction was negative.

The vomiting persisted and resulted in repeated episodes of severe dehydration, which responded to 0·9% saline subcutaneously or 0·18% saline intravenously. At one month it was found that there was gross sodium deficit and a raised serum potassium. Adrenogenital syndrome was suggested, but pigmentation was noted.

The electrolyte imbalance was corrected and controlled, at first with 3N saline which was given intravenously, and subsequently oral doses of salt of 7·5 gm. daily.

Investigation of adrenocortical function showed that the 17-ketosteroids were not elevated. ACTH intramuscularly produced no fall in the eosinophil count, nor an increase in the 17-ketosteroid excretion.

Cortisone was then added to the daily salt intake. Growth proceeded satisfactorily and the pigmentation was diminishing. In an attempt to control the continued salt loss, 9 alpha-fluorohydrocortisone has been added to the regime.

(To be published in greater detail elsewhere.)

Hepato-Lenticular Degeneration (Wilson's Disease).—J. J. KEMPTON, M.B.E., M.D., M.R.C.P., D.C.H.

V. S., boy aged 13.

History.—In August 1956 he fell and fractured a tibia. When the plaster was removed two months later he was noticed to be slow and stiff in his movements. Later his speech became indistinct, and it was on account of this that he saw his doctor in December 1956.

Four other children (half-brothers) and the father are healthy. The mother died of pneumonia in his early childhood.

On examination.—He shows all the appearances of hepato-lenticular degeneration. This is a striatal limb rigidity and fixity of facial expression. He adopts odd fixed postures, and has a tremor of tongue. His speech is slurred and indistinct. There are outbursts of spontaneous "thalamic" laughter. His tendon reflexes are normal. There is some gynæcomastia, and he has early clubbing of the fingernails, and very many spider nævi. The liver edge is hard and a little tender, and easily felt. Kayser-Fleischer rings are present in his corneæ.

Investigations.—Liver function tests indicate a severe degree of damage. Paper partition chromatography shows an excess amino-aciduria. His serum copper is abnormally low, 45 micrograms per 100 ml., with absent oxidase.

Treatment and progress.—Treatment has consisted of two courses of dimercaptal, and potassium sulphide given continuously in doses of 20 mg. thrice daily. He appears to have improved a little during three months' treatment.

Investigation of relations has shown that a great-aunt and great-uncle died of the disease. One cousin, aged 13, has amino-aciduria, minimal chemical evidence of liver damage, and very early pigment deposit in the cornea, shown on slit-lamp examination. Her serum copper is normal. She is quite symptom-free.

Cutis Laxa.—M. E. CASHMAN, M.B., Ch.B., D.C.H. (for J. J. KEMPTON, M.D., M.R.C.P.).

I. S., girl aged 18 months.

She is a first child of healthy parents, a full-term baby born following a normal pregnancy. The skin condition was noted at birth. There is no significant family history.

She was admitted to hospital at the age of 5 months with pneumonia, and has had

repeated respiratory infections since then. She has been in hospital five times in all, and there are persisting X-ray changes in the right lung.

Investigations show a normal blood picture and serum cholesterol, radiologically normal bones and epiphyses, and a normal ECG; fæcal trypsin is present, and sweat electrolytes are normal. A barium swallow shows free reflux, but no hiatus hernia.

At 18 months she is developing well. She walks and runs, feeds herself, says a few words and plays happily,

The appearance of the skin is grotesque (Figs. 1 and 2) but the texture is essentially normal. It is not hyperelastic, does not show any hæmorrhagic tendency and is not unduly friable.



FIG. 1.



FIG. 2.

Cutis laxa was first described by Alibert in 1832. In most standard textbooks of dermatology it is not clearly differentiated from cutis hyperelastica. Andrews (1946) described the two conditions separately. He says cutis laxa may occur as an isolated congenital anomaly, or in association with and secondary to Von Recklinghausen's disease or acromegaly. It is, of course, in some degree part of the facies of old age. The best clinical description of the condition is found in the standard French text book of dermatology by Dugos (1953). "La dermatolysie se caractérise par une flaccidité considérable de la peau (cutis laxa) qui forme de larges plis, flasques, mous, retombant en 'tablier'. La peau est de couleur normale. Elle est mobile, n'adhérant pas aux plans profonds. Elle a perdu toute élasticité et les plis produits par la traction ne se défont que lentement."

This child is presented both because of the intrinsic interest of a rare congenital abnormality, and because it is questioned whether there may be some association between the skin condition and the recurrent chest infection.

PS. (27.8.57).—Operation for inguinal hernia revealed an opportunity for skin biopsy and we are grateful to Dr. I. W. Whimster for the following report on histology:

"This shows a quite remarkable degree of elastic tissue abnormality, consisting of gross fragmentation, clumping, and curious granular degeneration. I have seen this kind of thing once or twice before but never on quite such a gross scale. The changes seem somewhat similar to those seen in senile skin, but much more exaggerated."

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PROCEEDINGS

of the

ROYAL SOCIETY OF MEDICINE

GOLDEN JUBILEE NUMBER

OCTOBER 1957

FOREWORD

by SIR FRANCIS WALSHE, O.B.E., M.D., F.R.S.

FELLOWS of the Society know that the Royal Society of Medicine arose from the amalgamation of some fourteen medical societies, and that fifty years ago, with a Royal Charter, it started on its new career. All this has been admirably described by Dr. Maurice Davidson in his recently published history of the Society—"The Royal Society of Medicine: the Realization of an Ideal"—and need not be recapitulated here.

What, perhaps, is less generally known is that many of the constituent societies published their own *Proceedings* or *Transactions* and that many, though not all, of these became merged in the *Proceedings* of the Society with which we are familiar. Comparisons are invidious, but it must be said that some of these earlier *Transactions* bore a high prestige and had been of primary importance in periodical medical literature for many years. Not a few major original contributions first saw the light in their pages, and references to some of them may still be encountered from time to time in modern papers. The *Transactions* of the Medico-Chirurgical Society, for example, formed an important element in world medical literature. To turn over some of the earlier nineteenth century volumes of the Society's *Transactions* is not only to encounter some classic original papers, but also to meet the predominance of a clear, concise and rhythmic English, written by men for whom the form of their papers was scarcely less important than their substance, and for whom to clothe their observations and ideas in worthy English was an ideal not forgotten.

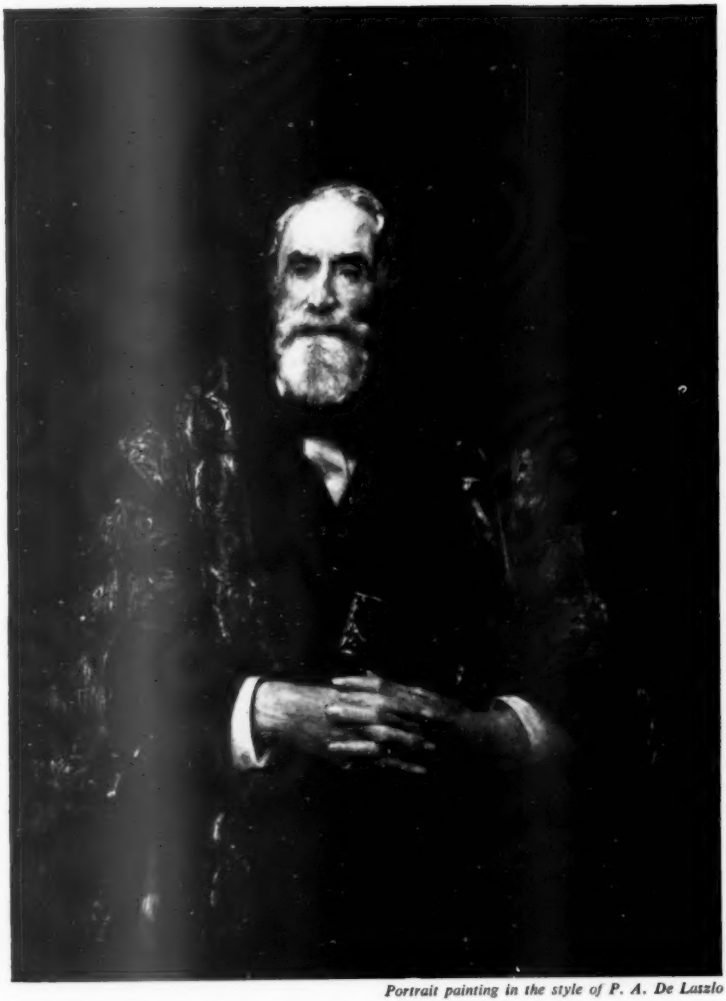
Thus, the *Proceedings* of our Society to-day has a distinguished tradition of scientific and literary excellence, the preservation of which has been the care of a long succession of devoted Honorary Editors, and also of the permanent editorial staff of the Society.

The expansion and increasing diversity of Medicine and Surgery have made the field of knowledge covered by the *Proceedings* almost more than they can adequately cope with, and the twenty-six Sections of the Society have to submit to limitations of space that, while regretted, have so far been inevitable.

Nevertheless, within these limited bounds, the *Proceedings* presents a balanced picture of the activities of its Sections, and if it be sometimes said that not every contribution breaks new ground in knowledge, the same is true of even the specialist journals, and it may be urged that no journal could continue in regular publication if it restricted the papers and communications it accepted to new discoveries of the first order. In fact, we know of no such journal.

Thus, the *Proceedings* reflects the different orders of medical and surgical work and thought: the original, the purely descriptive and clinical, the technical and methodological, and, at times, the critical review. These are the balanced diet of the medical reader, if we may use this simple metaphor, upon which he thrives.

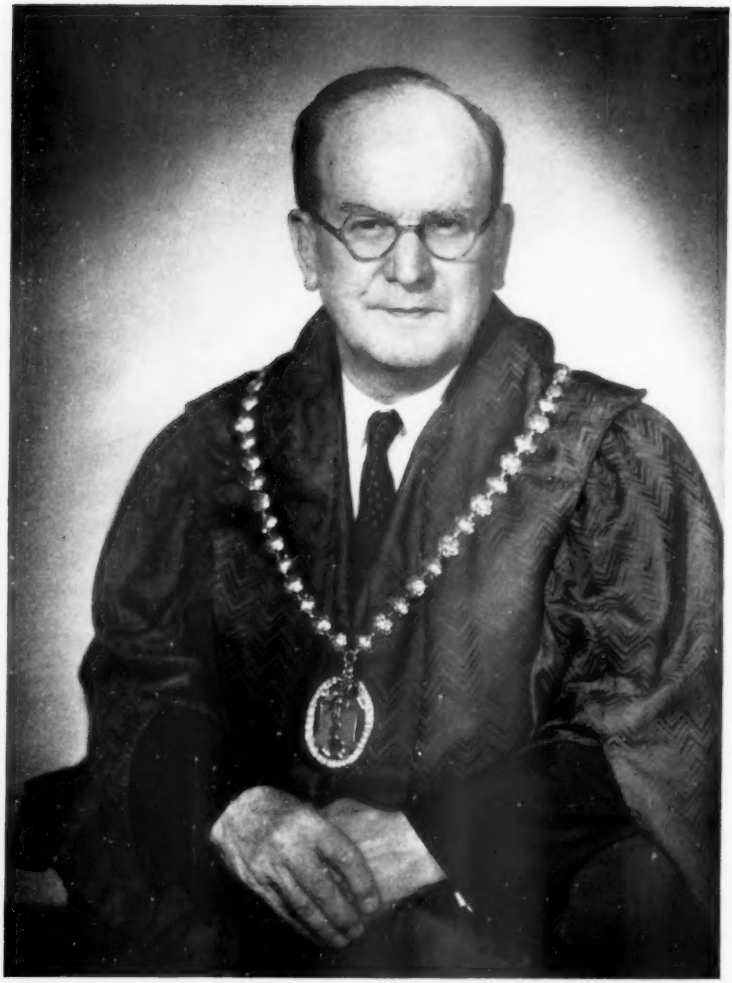
So to speak of our *Proceedings* betrays no spirit of complacency, for we can never be satisfied until it reflects the highest level of medical and literary excellence which the combined efforts of contributors and editors can achieve. It is in this spirit of determination to enhance the value and the appeal of our *Proceedings* that the Society enters upon its second half-century.



Portrait painting in the style of P. A. De Laszlo

SIR WILLIAM SELBY CHURCH, BT., K.C.B., M.D.
(1837-1928)

First President of the Royal Society of Medicine,
elected after the Amalgamation, 1907



Photograph by Douglas Glass

SIR CLEMENT PRICE THOMAS, K.C.V.O., F.R.C.S.

President of the Royal Society of Medicine, 1957
(elected 1956)

INTRODUCTION

by E. C. WARNER, M.D., F.R.C.P., and SELWYN TAYLOR, M.Ch., F.R.C.S.
HONORARY EDITORS

THE present Number of the *Proceedings of the Royal Society of Medicine* celebrates the completion of fifty years of publication. It will therefore be of interest to Fellows, Members and Associates of the Society to have a short account of the development and growth of this Journal.

The first number was published in November 1907. In a report of a meeting of the General Committee of Representatives of the Societies held on July 17, 1906, we read:

> There shall be ten monthly issues of a publication to be called "The Proceedings of the . . . Society".
>
> The "Proceedings" shall contain as full a record as possible of the society's work during the previous month.

The first pages of Volume 1 are devoted to the Presidential Address of Sir Thomas Barlow to the Clinical Section of the Society—a Section which was the lineal representative of the Clinical Society of London which had already been in existence for nearly forty years. The presentation of patients of particular clinical interest to the Fellows of the Society, and the subsequent discussions in which all can join, has always been a particularly interesting feature of the work of the Society.

The production of these earlier volumes reveals the great care which was taken not only with the text but also with the reproduction of photographs and drawings; this set a standard which has been adhered to even in times of World Wars and which compares very favourably with the pages of any journal being published to-day.

There is, however, one noticeable difference between Volume 1 and Volume 49: Volume 1 contained 2,548 pages, for in 1907 it was possible to publish almost verbatim the whole of the transactions of the 13 Sections of the Society. The large print of Volume 1, which gave 500 words per page, is still much more pleasing to the eye than the closely printed pages which, perforce, have had to be adopted since. In contrast to this, Volume 49 contains 1,080 pages and gives an account of the work of 26 Sections, which in the course of the year have held some 185 meetings. Regrettably this has meant that only about three-quarters of the meetings can now be reported, and the published account of each meeting has to be carefully scrutinized beforehand by the Sectional Editor and by the Honorary Editors, to save space whenever possible.

The selection of papers to be published to-day is necessarily a difficult and often an invidious task. Particular attention is paid to the fact that the majority of readers are in active clinical practice and cannot possibly attend more than a small number of the meetings held. The *Proceedings* enables them to keep in touch with the views of those who are expert on a particular subject, as well as with recent advances in our knowledge. The papers which do not see the light of day in the *Proceedings* are usually of a very special nature which are more suitable for publication in specialist journals.

The number of copies printed has steadily increased. In the first few years about 3,000 copies were distributed; after thirty years this rose to 5,000 copies and

now to 10,400 copies per month. The distribution is not only to Fellows of the Society in Great Britain; some 2,500 copies are sent overseas, including 70 presented to other institutions, 340 exchanged for other journals and 500 to outside subscribers.

Clearly the Royal Society of Medicine can enter the second fifty years of its publication of the *Proceedings* with every confidence. In the near future an innovation will be to publish the accounts of the special conferences to be organized by Council, at which leading authorities from at home and abroad will debate clinical topics of wide interest. Those engaged in original work will be encouraged to discuss their results in the various Sections of the Society with a view to obtaining early publication in the *Proceedings*.

The success of this publication over the years, and the success of this our Jubilee Number is largely due to the keenness and high standards of work of our permanent editorial staff, and it is to them that we give thanks for the production of this Number.

Proceedings of the Royal Society of Medicine

Vol. 50
725

Section of Experimental Medicine and Therapeutics

President—Professor C. A. KEELE, M.D., F.R.C.P.

[*December* 11, 1956]

WALTER ERNEST DIXON MEMORIAL LECTURE

[Number 8]

Ion Movement and Cardiac Fibrillation

By J. HAROLD BURN, M.D., F.R.S.

Department of Pharmacology, University of Oxford

Acetylcholine and atrial fibrillation.—In 1907 Walter Ernest Dixon, in whose memory this lecture is given, described experiments which he had carried out on the heart. In pithed animals he stimulated the vagi for half an hour and then extracted the heart. The extract possessed the power of inhibiting the frog's heart, and the inhibitory effect was abolished by atropine. He said also that "hearts treated in an identical manner, but in which the vagus nerve had not been excited, also gave a supply of this inhibitory substance, but in a smaller degree than in the excited heart". In the past few years we also have obtained evidence that the isolated heart, not receiving vagal impulses, liberates acetylcholine, and have described a series of observations which indicate further that acetylcholine has an action which is excitatory, though normally this action is not seen. It can be demonstrated in the isolated atria in the presence of drugs like quinidine, or when the atria are approaching exhaustion after long immersion in the organ bath, or when they are cooled (for references, *see* Burn, 1956). Recently, however, we have observed that in the heart-lung preparation of the dog where conditions are close to normal, acetylcholine can maintain the state of excitation commonly described as fibrillation. During experiments in which we infused acetylcholine at a constant rate, we discovered that when the right atrium was stimulated, the atria fibrillated. This fibrillation persisted after the stimulation stopped for as long as the infusion continued. Fibrillation was always recognized from the ECG, but evidence of the arrhythmia could also be seen in the record of the blood pressure. Fig. 1

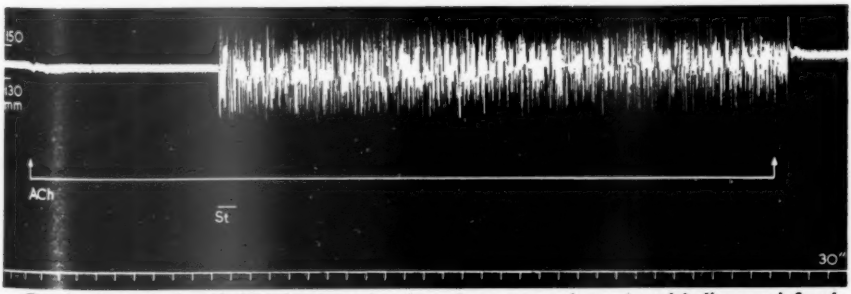


FIG. 1.—Record of aortic blood pressure in a heart-lung preparation. Acetylcholine was infused at a rate of 1 mg. per min., during the period shown. The tip of the right atrium was stimulated at a rate of 750/min. for 30 sec. at St. This produced atrial fibrillation which persisted until the acetylcholine infusion was stopped.

shows that the infusion of acetylcholine did not cause fibrillation until stimulation was applied; the application was for 30 sec. only, but the fibrillation continued until the infusion of acetylcholine was stopped 14 minutes later (Burn, Vaughan Williams and Walker, 1955*a*).

We have found that, to be certain of obtaining fibrillation, stimulation is required at a rate of 750 per minute. We use square wave pulses of 1 mA strength and 0·9 msec. duration. The length of time for which stimulation is applied appears to be relatively unimportant; 2 sec. may be long enough but we commonly use 30 sec. The amount of acetylcholine which

must be infused per min. to maintain fibrillation indefinitely varies in different preparations from 40 μg. to 4 mg. The effect of infusing different amounts in one preparation is shown in Table I, from which it is seen that if the rate of inflow of acetylcholine is less than a certain

TABLE I.—ATRIAL FIBRILLATION PRODUCED BY ELECTRICAL STIMULATION DURING INFUSION OF ACh

Rate of ACh infusion per min.	Duration of fibrillation after stimulation stopped
mg.	min.
0·4	0
0·6	0·58
0·8	1·16
1·0	4·0
1·1	6·0
1·2	10·0+

figure, the fibrillation established by stimulation does not last more than a few minutes. Our observation that under certain circumstances acetylcholine precipitates atrial fibrillation is not in itself new. Nahum and Hoff (1940) produced atrial fibrillation by applying acetyl-β-methylcholine to localized regions on the atrial surface, and it has long been known that vagal stimulation, which releases acetylcholine, favours the occurrence of atrial fibrillation.

Fibrillation in the presence of an anticholinesterase.—The addition of an anticholinesterase to the heart-lung preparation causes the accumulation of acetylcholine in the blood, and this accumulation was observed to be greater when the heart was driven electrically by stimuli applied either to the atria or to the apex of the ventricle (Burn, Vaughan Williams and Walker, 1956). We therefore tried stimulation of the atria in the presence of eserine and also of paraoxon (Mintacol) to see if fibrillation would occur when cholinesterase was inhibited. Most of our experiments were made with paraoxon, which is an organic phosphate having an action of longer duration than that of eserine. We found that fibrillation was induced by stimulation, and lasted after stimulation for a time which was proportional to the amount of paraoxon present, as shown in Table II. In one trial fibrillation was maintained for 25 min. (Burn, Vaughan Williams and Walker, 1955*b*).

TABLE II.—PRODUCTION OF ATRIAL FIBRILLATION BY ELECTRICAL STIMULATION WHEN PARAOXON WAS ADDED TO THE BLOOD IN DIFFERENT CONCENTRATIONS

Experiment	Molar concentration	Rate of stimulation per min.	Duration of fibrillation when stimulus stopped
1	9×10^{-6}	556	1 min.
	$1{\cdot}8 \times 10^{-5}$	556	3·3 min.
	$3{\cdot}6 \times 10^{-5}$	562	9·6 min.
2	9×10^{-6}	330	5 min.
	$2{\cdot}7 \times 10^{-5}$	750	25 min.
	10^{-4}	1,256	(Stopped by atropine)
3	9×10^{-6}	708	(Flutter 10 sec.)
	$2{\cdot}7 \times 10^{-5}$	875	1 min.
	$6{\cdot}3 \times 10^{-5}$	865	10 min.

Fibrillation due to aconitine.—The substance aconitine was introduced by Scherf *et al.* (1948) as a means of causing atrial fibrillation. An amount of 25 μg. is injected under the epicardium of the tænia terminalis, or a 5% solution in benzene is applied to one small area of the atrial surface. In the anæsthetized dog where vagal control is present, atrial fibrillation occurs. In the heart-lung preparation in which the vagi are cut, we found that the injection of aconitine alone did not cause fibrillation in the few experiments in which we tried, but that it did so with regularity after the addition of eserine to the blood. On the other hand, it never caused fibrillation in the presence of atropine; its effect then was to produce a tachycardia, accompanied by some degree of A–V block. These findings led us to conclude that atrial fibrillation due to aconitine depended for its occurrence on the presence of acetylcholine, the aconitine producing an ectopic focus from which a series of impulses arose, corresponding to the electrical stimuli which were required to start the fibrillation in the absence of aconitine.

Conversion of tachycardia into fibrillation.—In a series of experiments we stimulated the atria during the infusion of adrenaline or noradrenaline into the blood at a constant rate. In the majority of trials, normal rhythm was observed when the stimulation stopped. In some trials, however, a tachycardia was established, which either reverted to normal rhythm after some minutes or persisted. When it persisted we observed that if an infusion of acetylcholine was given, atrial fibrillation then promptly developed.

Factors required for atrial fibrillation.—We thus produced atrial fibrillation (1) by brief electrical stimulation of the atria during the infusion of acetylcholine, (2) by electrical stimulation of the atria after the addition of eserine or paraoxon to the blood, (3) by the injection of aconitine into the tænia terminalis after the addition of eserine to the blood, and (4) by the infusion of acetylcholine after establishing a tachycardia. The common factors in these different circumstances were the presence of acetylcholine in the blood and a high rate of stimulation. The acetylcholine produced a condition in the atria in which fibrillation occurred whenever a rapid succession of stimuli was applied; these might be electrical or they might arise from an ectopic focus set up by aconitine or they might be the tachycardia set up by stimulation during the infusion of adrenaline.

Fibrillation in isolated atria.—Fibrillation has also been established in isolated atria by my colleague W. C. Holland (Holland *et al.*, 1957). He dissected the atria from a freshly excised rabbit heart and suspended them in an isolated organ bath at 29° C. in which they were well oxygenated. A pair of electrodes penetrated the atria through which stimulation could be applied at one time and an ECG record could be taken at another. Holland failed to establish fibrillation by stimulating the atria in normal Locke's solution even in the presence of acetylcholine. However, when the K^+ concentration was reduced from 5·6 mM/l. to 1·4 mM/l., he then found that fibrillation occurred as shown in Fig. 2 and that the fibrillation stopped when the acetylcholine was removed from the bath. He demonstrated further that the fibrillation was arrested by atropine.

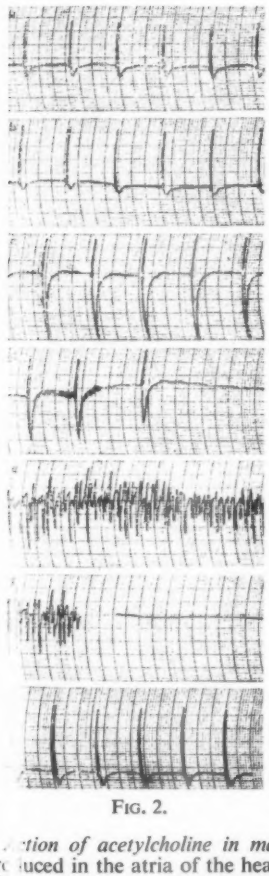


FIG. 2.

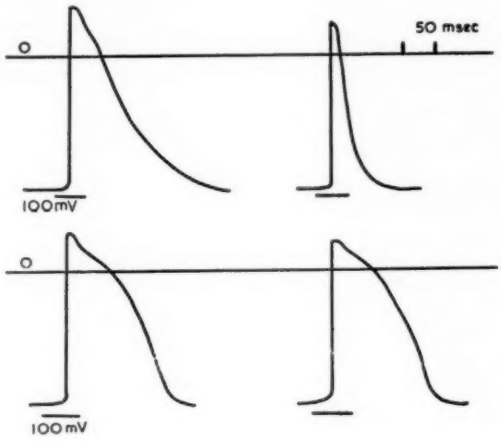


FIG. 3.

FIG. 2.—ECG records taken from isolated atria in bath of Ringer's solution. a, in normal Ringer's solution; b, in Ringer containing 1·4 mM/l. potassium; c, after stimulation for 2 min., d, after addition of acetylcholine which arrested the beat; e, after stimulation in the presence of acetylcholine; f, fibrillation stopped by atropine; g, in normal Ringer. (Holland and Burn, 1957.)

FIG. 3.—To show the effect of acetylcholine on the action potential. The upper records are from the atria and the lower records from the ventricles. Records on the left are control records; those on the right are in the presence of acetylcholine. (Drawn from records of Hoffman and Suckling, 1953, *Amer. J. Physiol.*, 173, 312.)

Action of acetylcholine in maintaining fibrillation.—As has been stated, the fibrillation produced in the atria of the heart-lung preparation by brief stimulation during the infusion of acetylcholine, was maintained until the infusion was stopped. This indicated that acetylcholine by itself maintained some change in the atria responsible for the continuation of

fibrillation. That acetylcholine shortens the refractory period of atrial tissue has long been known, and recent observations have provided more information about this effect. To understand it, the movements of ions into and out of the cell require consideration.

The membrane of a cell is relatively impermeable to sodium ions and is the seat of chemical processes which drive Na^+ out of the cell, so that the concentration inside is less than that outside. These processes constitute what Hodgkin (1951) has called the sodium pump. For potassium ions the situation is reversed and the concentration inside the cell is much greater than that outside. As a consequence the cell membrane bears an electrical charge which is negative internally and positive externally. Thus, if a micro-electrode is placed inside an atrial cell of the dog during diastole, a negative charge of about 90 millivolts is recorded.

When a stimulus arrives at the cell membrane the membrane becomes permeable to sodium ions. In consequence Na^+ moves into the cell rapidly, and the internal negative potential falls abruptly being reversed to a positive potential of about 30 mV. This fall of the internal potential is spoken of as the rising limb of the "action potential". About the time that the entry of Na^+ has neutralized the internal charge on the membrane, at which point the membrane is said to be depolarized, K^+ begins to diffuse out of the cell, and by doing so begins to restore the charge on the membrane. Cardiac muscle cells differ from those of nerve because the restoration of the charge on the membrane takes place slowly, so that the descending limb of the action potential is not abrupt, but is gradual. In its early course the limb may not descend at all, but may appear as a plateau, at the end of which repolarization takes place rapidly, and the action potential is then complete. For the greater part of the period of the action potential the cell is inexcitable; towards the end, however, the refractory period finishes. The Na^+ which enters the cell when a stimulus arrives is afterwards driven out by the sodium pump. Similarly, the K^+ which leaves the cell during repolarization is carried back into the cell by chemical processes which are in part at least linked to the sodium pump, occurring only when the sodium pump is working.

The first evidence that the action potential in the atrium was affected by vagal inhibition was obtained by Samojloff (1914) who showed that it was shortened. More recently Burgen and Terroux (1953) and Hoffman and Suckling (1953) have studied the changes by the use of intracellular electrodes. They are shown in Fig. 3. Both investigations revealed that the effect of acetylcholine upon the action potential was to accelerate the rate of repolarization, that is, to make the downstroke much steeper. Burgen and Terroux suggested that acetylcholine made the membrane more permeable to K^+, since the downstroke is determined by the exit of K^+ from the cell. Trautwein *et al.* (1956), working on isolated strands from frog auricles, have shown that during inhibition by acetylcholine the conductance of the muscle membrane is increased. Harris and Hutter (1956) have found that when the sinus venosus and the atria of the frog or tortoise heart were loaded with ^{42}K, the rate of loss of the isotope was increased by acetylcholine two or three times. Furthermore, they showed that the rate of uptake of ^{42}K was also increased. In the investigation already mentioned Holland has studied the loss of K^+ in isolated rabbit atria when he applied stimulation at increasing rates. In control observations the rate of K^+ rose only from 3·8 to 4·7 mM/kg. wet tissue per 5 min. when the stimulation was raised from 200 to 1,200 per min. In the presence of acetylcholine ($3{\cdot}0 \times 10^{-4}$g./ml.), however, the rate of loss rose from 6·8 to 10·5 mM as the rate of stimulation increased from 200 to 800 per min., and fibrillation occurred when the loss of K^+ exceeded a value about 10·5 mM/kg. wet tissue per 5 min. This was observed when the rate of stimulation was 600 per min. or more (Holland, Burn and Schümann, 1957).

Hence the maintenance of atrial fibrillation appears to be linked to the diminution in membrane resistance, to the increased permeability to K^+ and to the increased rate of loss of K^+ which acetylcholine causes. Thus it seemed likely that fibrillation would be arrested by measures which retarded the outflow of K^+ from the cells and which prolonged the repolarization of the action potential.

Effect of raising the extracellular K^+.—The simplest method of retarding the outflow of K^+ seemed to be to raise the concentration of extracellular K^+. (Whether this idea was justified will be discussed later.) In a series of experiments in which we established atrial fibrillation in the heart-lung preparation as already described, we infused a solution of KCl slowly at a constant rate. We found this infusion arrested the fibrillation after amounts from 50 to 410 mg. had entered the blood, the mean amount being 227 mg. There was approximately 1 litre of blood in the system, so that the K^+ concentration was raised from 5 to 8 mEq./l. Not only was fibrillation arrested in spite of continued infusion of acetylcholine, but when attempts were made to re-establish it by further stimulation it was found impossible to do so (Burn, Gunning and Walker, 1956).

Effect of adrenaline.—Having supported the hypothesis by showing that infusion of KCl would arrest fibrillation, we turned our attention to a study of the effect of adrenaline. The injection of adrenaline into animals anæsthetized with chloroform was shown by Levy (1912)

to precipitate ventricular fibrillation, and anæsthetists have long regarded adrenaline as a substance which is dangerous for this reason. However, it seemed possible that a different relation might be revealed in the atria. Webb and Hollander (1956), having confirmed that acetylcholine shortened the duration of the action potential in the isolated atria, found that adrenaline prolonged it by a mean figure of 14%. The effect of adrenaline in the heart-lung preparation is certainly complex, and we were not surprised to find that in different experiments different results were obtained. However, out of a total of 16 experiments, we observed that an infusion of adrenaline or noradrenaline prevented atrial fibrillation from being established in 9. In 2 experiments we observed the opposite result, and in 5 experiments we observed no effect.

An example of the prevention of fibrillation is given in Fig. 4, taken from the kymograph

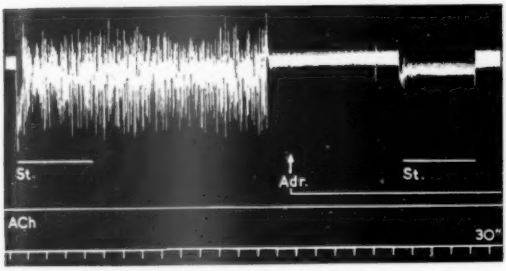


FIG. 4.—To show the action of adrenaline in preventing fibrillation. Acetylcholine was infused throughout the record. Stimulation was applied to the right atrium at "St", and this caused fibrillation which reverted to normal rhythm after 4·5 min. Adrenaline was then infused in addition to acetylcholine. Stimulation now failed to cause any fibrillation.

record. During infusion of acetylcholine alone, stimulation of the right atrium produced an arrhythmia which the ECG showed to be fibrillation. During the infusion of adrenaline and acetylcholine together, there was no arrhythmia. This result and the similar results in 8 other experiments were consistent with the view that adrenaline prevented acetylcholine from causing fibrillation by preventing repolarization from being sufficiently rapid, and the refractory period from becoming sufficiently short.

Arrest of fibrillation by quinidine.—The action of quinidine in arresting atrial fibrillation has long been attributed to a lengthening of the refractory period, in other words, to an increase in the duration of the action potential. Recent observations by Armitage (1957) indicate that this increase may be due to a decrease in the permeability of the membrane to K^+, though this is not yet proved. When the isolated atria are suspended in a bath, the addition of quinidine to make a concentration of 10^{-5} causes a progressive diminution in amplitude and rate of beat until it stops. The beat can be started again in two ways; either by adding acetylcholine to the bath, or by reducing the concentration of K^+ in the solution. Since we know that acetylcholine increases the permeability of the membrane to K^+ it would appear that quinidine may act by diminishing the permeability of the membrane to K^+. This is supported by the evidence that reduction of the K^+ in the external fluid also neutralizes the effect of quinidine, for this reduction by increasing the concentration gradient from inside to outside would offset the diminution in permeability.

VENTRICULAR FIBRILLATION

The study of ventricular fibrillation.—In the whole animal or in the heart-lung preparation, the onset of ventricular fibrillation brings the circulation to a standstill. To study fibrillation it was necessary to use a system in which the coronary flow continued although fibrillation had begun, and for this the simplest arrangement was the isolated rabbit heart perfused through the aorta, by Langendorff's method. Grumbach *et al.* (1954) have used this preparation and observed that in it ventricular fibrillation occurred spontaneously when it was perfused with a solution free from potassium, though not if calcium was also absent. They also observed fibrillation if they injected large doses of calcium. In our experiments we produced fibrillation by electrical intraventricular stimulation. When the heart was perfused with a modified Krebs' solution containing 5·6 mM/l. K^+ and 2·2 mM/l. Ca^{++} and the ventricles were stimulated at increasing rates, fibrillation began at a rate near 600 per min. If this rate of stimulation was then maintained for a fixed period of 5 min., when the stimulation stopped, the ventricles continued to fibrillate. This might be for a short period, reversion to normal rhythm occurring within 5 min. or it might be for 30 min. after which observation was discontinued. An arbitrary distinction was made between these hearts, the former being said not to fibrillate and the latter being counted as fibrillating. Of 28 hearts studied at 36°–37° C., perfused with the solution described, 11 were found to fibrillate in this sense.

Effect of carbachol and atropine.—Since acetylcholine produced a condition in the atria in

which stimulation caused fibrillation, the effect of adding carbachol (the carbamic ester of choline) to the perfusion fluid was studied. Experiments in 11 hearts failed to show any effect of carbachol in a concentration of $1{\cdot}25 \times 10^{-6}$g./ml. A similar negative result was obtained when atropine was added in concentrations up to 10^{-6}g./ml. Thus the ventricles differed from the atria in this respect. Hoffman and Suckling (1953) found that acetylcholine did not shorten the duration of the action potential in the ventricle.

Changes in potassium ions.—Because of the results obtained with atrial fibrillation, observations were first made to determine the effect of changes in the concentration of K^+ in the perfusion fluid. The proportion of hearts which fibrillated fell when the concentration of K^+ was raised; at twice the normal concentration no heart fibrillated even during the period in which the stimulation was applied. As the concentration of K^+ was reduced the proportion of hearts which fibrillated rose as shown in Table III until at a concentration one-quarter the normal, 5 out of 6 hearts fibrillated spontaneously without electrical stimulation.

An illustration is given in Fig. 5.

TABLE III.—EFFECT OF CHANGES IN K^+ CONCENTRATION ON PROPORTION OF HEARTS FIBRILLATING

K^+ concentration mM/l.	Proportion of hearts fibrillating	Percentage
11·2	0 out of 7	0
5·6	11 „ „ 28	39
4·2	20 „ „ 26	77
2·8	10 „ „ 11	91
1·4	6 „ „ 6	100

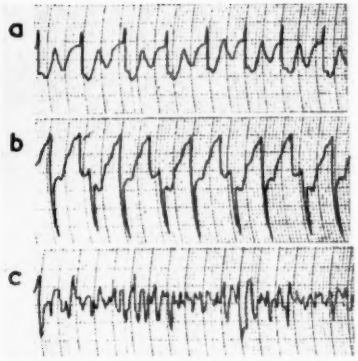


FIG. 5.—ECG record from ventricles of isolated heart. a, taken after changing to perfusion fluid with only 1·4 mM/l. potassium; b, taken 20 min. later; c, showing spontaneous fibrillation 5 min. after b.

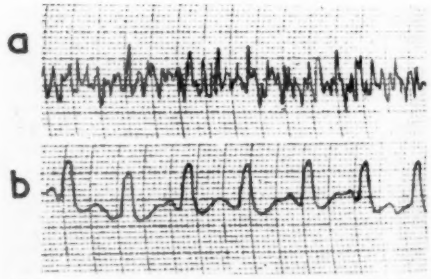


FIG. 6.—ECG record from ventricles (a) fibrillating in low calcium Ringer 0·07 mM/l. The Ringer was then changed to calcium-free Ringer, when the fibrillation stopped, as shown in (b).

The effect of reducing the potassium concentration was abolished by a simultaneous reduction of the calcium concentration. When the perfusing solution contained one-quarter calcium as well as one-quarter potassium, fibrillation did not occur, but on raising the calcium to normal, fibrillation occurred once more. The results with low potassium were of special interest since they showed that normal rhythm could change to fibrillation without the intervention of electrical stimulation.

Changes in calcium ions.—Observations were then made to determine the effect of changes in the concentration of calcium. In general it was found that the proportion of hearts which remained in persistent fibrillation was affected in the opposite direction to that in which it was affected by changes in potassium. When the concentration of calcium ions was raised to twice the normal, all hearts fibrillated. At the other extreme, when the solution perfusing a heart which was fibrillating was changed to one which was Ca-free, the fibrillation was arrested as shown in Fig. 6. Between these extremes there was no simple gradation of the calcium ion concentration changed, as is shown in Fig. 7. Up to concentrations of 0·3 mM/l., the proportion of hearts fibrillating steadily increased; above this concentration, however, the proportion declined until the concentration reached 2·2 mM/l.; finally, as already stated, at 4·4 mM/l. all hearts fibrillated. A similar change with rise of calcium ion

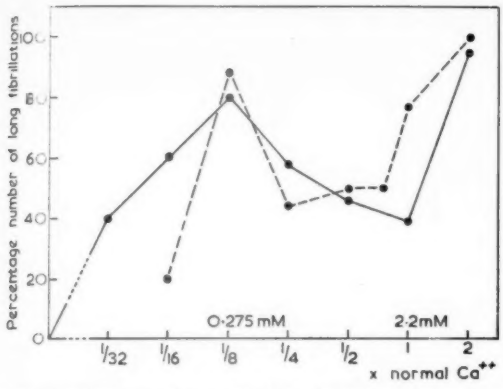


FIG. 7.—Chart showing the relation between the proportion of hearts fibrillating for 30 min. after stimulation and the amount of calcium in the perfusion fluid. The full line shows the relation with 5·6 mM/l. potassium. The broken line shows the relation with 4·2 mM/l. potassium. The full line was determined on larger numbers of hearts than the broken line.

concentration was observed when the solutions contained 4·2 mM/l. K^+ as when they contained 5·6 mM/l. K^+.

Effect of reducing sodium ions.—Experiments were carried out in which the sodium ion concentration was reduced by one-half, and it was found that in all of them stimulation caused persistent fibrillation. In 13 experiments the tonicity was maintained by the addition of sucrose; this meant that the concentration of chloride ions was reduced as well as that of sodium ions. In 7 further experiments the tonicity was maintained by choline chloride, giving atropine to prevent A–V block. The concentrations of potassium and of calcium ions were normal. Thus, reducing the sodium ions to half increased the proportion of hearts fibrillating from 40 to 100%.

Loss of potassium during fibrillation.—An increased loss of potassium ions during fibrillation was directly observed. By the use of a Beckman flame photometer the potassium content of the fluid leaving the heart was determined before fibrillation was induced, during fibrillation and then again when a normal rhythm had been restored for 15 min. It was found that the loss of potassium was greater during fibrillation whether this was induced in the presence of a lowered potassium content of the perfusing fluid, a raised calcium content or a lowered sodium content. Results are shown in Table IV.

TABLE IV.—INCREASE IN K^+ LOSS DURING FIBRILLATION

Perfusion fluid	No. of hearts	Mean K (mg./l.) of perfusing fluid leaving the heart		% increase in K concn. during fibrillation
		Before and after fibrillation	During fibrillation	
½× normal K^+	5	112·5	121·9	8·0
2 × normal Ca^{++}	5	203·1	207·9	2·3
½× normal Na^+	5	217·2	221·9	2·2

Action of adenosine triphosphate.—The addition of adenosine triphosphate to the solution perfusing the heart was found to arrest fibrillation in a high proportion of hearts as is illustrated in Fig. 8. This substance (A.T.P.) was tested because it is known to be an energy

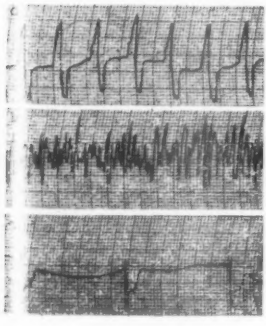


FIG. 8.—ECG records of ventricles. a, in normal Ringer; b, after production of fibrillation by stimulating in fluid containing 4·2 mM/l. potassium and 3·3 mM/l. calcium. The fibrillation persisted after stimulation stopped for 14 min. until A.T.P. was added to the perfusion fluid. This arrested the fibrillation, as shown in c.

donor, and by its means the rate of replacing potassium ions within the cell might be increased. The addition of A.T.P. to the perfusing solutions would not, however, increase the amount of A.T.P. *within* the cell, so that it is unlikely that it could act in this way. Fortunately, this was not realized before it was discovered that A.T.P. did, in fact, arrest fibrillation. In one experiment in which a heart was fibrillating in a solution containing normal concentrations of potassium and calcium, the addition of A.T.P. in a concentration of $2{\cdot}5\times10^{-5}$M converted fibrillation to a tachycardia; the solution was then changed to a solution without A.T.P. and the fibrillation was resumed; with a higher concentration of A.T.P. ($6{\cdot}4\times10^{-5}$M) the fibrillation reverted to normal rhythm, and on changing back to a solution without A.T.P., the normal rhythm once more gave place to fibrillation. Finally, the solution with A.T.P. again restored a normal rhythm. It seemed in this experiment that A.T.P. was a key substance in controlling fibrillation.

Action of magnesium ions.—The observations with solutions containing varying proportions of calcium ions had shown that an excess of calcium ions caused fibrillation. Since A.T.P. can enter into combination with calcium ions and thus neutralize their activity, it was possible that A.T.P. arrested fibrillation by such a combination, which might occur within the pores of the cell membrane. If this were true it seemed that it should be possible to demonstrate that magnesium ions potentiated the action of A.T.P. since magnesium ions might be required to link the A.T.P. to the protein in the membrane. Experiments were carried out on hearts in which fibrillation was produced by stimulation during perfusion with a solution containing 4·2 mM/l. of K^+ and 0·275 mM/l. of Ca^{++}. It was found that when the solution was changed to one containing $6{\cdot}4\times10^{-5}$M A.T.P., the fibrillation was not arrested, but on changing to a solution containing $1{\cdot}6\times10^{-6}$M Mg^{++} in addition, the fibrillation was arrested in 4 out of 7 experiments.

Effect of Versene and A.M.P.—A substance which is known to bind calcium ions, and thus to inhibit their activity is ethylenediamine tetra-acetate or Versene. It was found that Versene would also arrest fibrillation, but this occurred only when the amount of calcium ions in the perfusion fluid was low and the concentration of Versene sufficient to remove all calcium ions from the solution.

Other phosphates, adenosine monophosphate or A.M.P. and inosine triphosphate were tested, and they also were found to arrest fibrillation in some experiments, though again only when the amount of calcium ions in the solution was low. We did not discover in these experiments whether all calcium ions were removed from solution, and whether the arrest of fibrillation was due to this cause. The results are shown in Table V.

TABLE V.—EFFECTS OF ADENOSINE TRIPHOSPHATE (A.T.P.), ADENOSINE MONOPHOSPHATE (A.M.P.), INOSINE TRIPHOSPHATE (I.T.P.) AND ETHYLENE DIAMINE TETRA-ACETATE (VERSENE)
Fractions are the proportion of hearts in which fibrillation was arrested

	Molar concentration	Millimolar calcium concentration 2·2–4·4	0·275–0·55
A.T.P.	$1{\cdot}6\times10^{-4}$	7/10	5/7
A.M.P.	$2{\cdot}9\times10^{-4}$	0/3	0/2
	$5{\cdot}8\times10^{-4}$	0/1	1/3
	$8{\cdot}7\times10^{-4}$		1/1
I.T.P.	$1{\cdot}6\times10^{-4}$	0/5	2/2
Versene	$3{\cdot}2\times10^{-4}$	0/4	5/7

The effect of dinitrophenol.—In the hope of obtaining a clue to the meaning of the results with A.T.P., to learn, that is, whether A.T.P. normally plays a role in the cell membrane, we investigated the action of 2,4-dinitrophenol which is said to uncouple oxidation and phosphorylation. The energy derived from oxidation is used in part to convert A.D.P. or A.M.P. into A.T.P. by adding one or two phosphate groups. In the presence of dinitrophenol (D.N.P.) the energy derived from oxidation cannot be used in this way, and A.T.P. cannot be formed. In consequence, if A.T.P. normally plays a part in preventing fibrillation, the addition of D.N.P. to the perfusion fluid should cause persistent fibrillation in conditions in which it would not otherwise occur.

In a series of experiments, shown in Table VI, carried out on hearts which did not fibrillate for more than 4 min. after stimulation, the addition of D.N.P. in a concentration 5×10^{-5}M caused them to fibrillate for periods from 15 to 35 min.; at the end of this time the perfusion was continued without D.N.P. and the hearts then reverted to normal rhythm. These results were obtained in solutions containing calcium both in higher and lower concentrations (Armitage *et al.*, 1957).

TABLE VI.—EFFECT OF 2,4-DINITROPHENOL

Duration of fibrillation after stimulation stopped

Exp. No.	Before D.N.P.	In presence of D.N.P.	Molar concn.
1	0 min.	16 min.	3×10^{-6}
2	1 „	>35 „	„
3	4 „	20 „	„
4	0 „	>22 „	5×10^{-6}
5	2 „	>15 „	„

DISCUSSION

The theory of auricular fibrillation which was almost universally accepted for about thirty years was that of a circus movement of an excitation wave around the large veins; this movement persisted so long as the refractory period of the auricular muscle was short (*see* Lewis *et al.*, 1918–20, 1921). In 1948 and 1950 Scherf and his colleagues published papers suggesting that rapid impulse formation in one or more centres was rather to be regarded as the underlying cause, and a similar conclusion was reached by Prinzmetal and his colleagues (1950). Ventricular fibrillation was studied by Moe *et al.* (1941); it was precipitated by a D.C. shock and was believed to be due to a re-entry of impulses attributable to a progressive decrease in refractory period combined with a progressive increase in conduction time.

All workers are bound to interpret phenomena in terms of the observations their methods allow them to make, and our study of the fibrillation in the ventricles of the isolated rabbit heart has led us to emphasize different aspects of fibrillation. Our general method has been to induce fibrillation by rapid stimulation of the ventricular muscle, and then to see how long it persisted when perfusion fluids of different composition were used. In the course of this work we have observed that rapid stimulation or indeed stimulation of any kind is not an essential factor in the production of fibrillation. Thus we have found that when the potassium concentration is reduced to 1·4 mM/l. the ventricles fibrillate spontaneously. The normal rhythm suddenly disappears and fibrillation begins. This result was obtained earlier by Grumbach *et al.* (1954). The fibrillation can be arrested by changing to a solution with a higher potassium concentration. Further, we have found that when the potassium concentration is 11·2 mM/l., no rate or duration of stimulation has ever produced fibrillation even while it was applied. Next we have observed that when fibrillation has been established, perfusion with A.T.P. caused reversion to normal rhythm, and subsequent return to a solution without A.T.P. once more brought back fibrillation. Finally, observations (Burn and Goodford, 1957) have shown that when fibrillation was established at 37°, cooling to 32° C. caused reversion to normal rhythm, and re-warming to 37° again caused fibrillation. Thus by lowering potassium concentration or by removing A.T.P. or by raising temperature the change from normal rhythm to fibrillation was induced, and the reverse procedures restored the normal rhythm. These results indicated not only that fibrillation is reversible, as was already known, but that it can be produced and arrested alternately by changing the composition of the fluid perfusing the heart without the use of electrical stimulation.

An attempt can be made to interpret these changes in terms of the movement of ions across cell membranes, or in terms of the part played by ions. We may first consider the effect of reducing potassium. There is normally a much greater concentration of potassium within the cardiac muscle cell than there is without, and the potential difference on the two sides of the membrane depends on the difference in concentration. When the external potassium concentration is reduced to one-quarter, this difference must be greatly exaggerated, so that perhaps because of this the insulating properties of the membrane break down, and it becomes unstable; thus the condition of fibrillation arises. However we have recently observed that this spontaneous fibrillation does not occur when calcium is also reduced to one-quarter, so that the spontaneous ventricular fibrillation may be due to a rise in the Ca/K ratio rather than to the fall in potassium.

Fibrillation can be arrested by adding A.T.P. to the perfusing fluid, and it can then be re-established without electrical stimulation by withdrawing the A.T.P. The part played by A.T.P. cannot be related to metabolic processes inside the cell since A.T.P. does not penetrate the interior of the cell. A.T.P. is known to combine with calcium ions, and it is possible that in abolishing fibrillation, A.T.P. is combining with calcium ions not within the cell but within the pores of the cell membrane. This idea assumes that fibrillation is caused by an excess of free calcium ions in the membrane and that it stops when this excess is removed.

The arrest of fibrillation by cooling from 37° to 32° C. is likely to be due to a lengthening of the refractory period. It has been observed by Hollander and Webb (1955) that a fall of

temperature prolongs the duration of the action potential in the atrium, which means that it prolongs the period in which the cardiac cells are inexcitable and so terminates the fibrillation. When the temperature is raised again we have observed that fibrillation reappears without electrical stimulation.

These examples illustrate in what terms three conditions may be discussed in which fibrillation can be converted to normal rhythm, and normal rhythm back again to fibrillation without intervention of electrical stimulation.

We may now consider atrial fibrillation produced by applying stimulation at a rate of 750 per min. during the infusion of acetylcholine. Attention has already been drawn to the evidence that acetylcholine can diminish the duration of the action potential (from between 150 and 200 msec. down to periods as short as 10 msec.), that it increases the membrane conductance and the permeability to potassium. Hoffman and Suckling (1953) also found that when a stimulus was applied in the presence of acetylcholine fairly early in the relative refractory period, it caused not one but a succession of action potentials of very short duration, sometimes lasting for 10 min., at rates of 700 to 1,500 per min. This has been confirmed by Dr. M. H. Draper (1956). In our experiments the rate of stimulation used was 750 per min., so that there was an interval of 80 msec. between stimuli, which might well arrive early in the relative refractory period, and so set up such a succession of action potentials.

The cause of the succession of action potentials has been discussed by Segers (1947) who stressed the importance of the supernormal phase of excitability first demonstrated in cardiac tissue by Adrian (1920). Segers pointed out that when several contractions follow one another sufficiently rapidly, each stimulus arriving during the supernormal phase following the preceding contraction, the supernormal phases pile up, the excitability steadily increases and the threshold of excitation falls until it disappears. Continuous depolarization and repolarization may then occur without a further stimulus.

Fibrillation persisted in the atria only so long as acetylcholine was infused, and the changes produced by acetylcholine were therefore essential for fibrillation. Of these the increased permeability to potassium would seem from Holland's observations to be of importance since he found that fibrillation occurred in the isolated atria only when the exchange of sodium and potassium ions exceeded 10 mM/kg. wet tissue per 5 min. This value was reached when stimulation was applied at rates of 600 per min. or more in the presence of 5×10^{-4}g./ml. acetylcholine. The addition of quinidine to the system inhibited both the fibrillation and the increase in the ion exchange.

The short duration of the action potential is clearly important for fibrillation, for if fibres in a given area are out of phase, they may stimulate one another so long as the duration of the action potential is short and the recovery of excitability is rapid. They may thus maintain the fibrillation. Hoffman and Suckling (1953) have suggested that the normal long action potential is maintained by metabolic processes which may delay repolarization, and that they are inhibited by acetylcholine. Since adrenaline increases the duration of the action potential and can prevent fibrillation due to stimulation in the presence of acetylcholine, it may do so by increasing these metabolic processes.

While it has been seen that ventricular fibrillation can be produced without electrical stimulation, most of our observations were made by inducing fibrillation by stimuli at the rate of 600 per min. upwards. Moe *et al.* (1941) observed that when they produced fibrillation by the application of a D.C. shock, the onset of fibrillation was preceded by discrete deflections at progressively decreasing intervals. The succession of action potentials evoked in the atria which have just been discussed seem to be a similar phenomenon.

The factors which have been shown to modify the proportion of hearts in which persistent ventricular fibrillation was observed are factors known to modify the duration of the action potential. Dinitrophenol, which shortens the action potential in the frog ventricle as shown by Macfarlane and Meares (1955) causes ventricles to fibrillate when they otherwise do not. A fall in temperature which has been shown to lengthen the action potential (Hollander and Webb, 1955) causes ventricles to cease fibrillating.

The action of calcium requires special consideration. As long ago as 1936 Schütz stated that in high-calcium solutions cardiac muscle becomes re-excitable at a relatively early stage of repolarization. This was confirmed by Weidmann (1955). Hoffman and Suckling (1956) found that in papillary muscle when the amount of calcium was high repolarization occurred at a faster rate, while when the amount of calcium was low the action potential was longer, due to a prolongation of the plateau. We found that high calcium solutions raised the proportion of hearts which fibrillated on stimulation.

The observations of Hoffman and Suckling (1956) on the effect of changes in calcium concentration on excitability in the auricles were of particular interest. They showed that when the calcium concentration was lowered, the change in auricular excitability was biphasic; at first the auricular tissue was more excitable, and then, below 0·27 mM/l, it was

less excitable. These changes are very similar to those in the proportion of hearts in which the ventricles fibrillated on stimulation (*see* Fig. 7). In skeletal muscle calcium stabilizes the membrane, and when calcium is reduced, spontaneous activity develops in the fibres. The increased tendency to fibrillation which is seen when calcium is lowered from 2·2 mM/l. to 0·27 mM/l. may be the corresponding change in cardiac muscle, occurring because the membrane becomes more permeable and its diminished resistance gives rise to greater excitability. If, however, the calcium is reduced below 0·27 mM/l., the leak of ions through the membrane perhaps becomes so great that many of the fibres are inexcitable, and so there is a decreasing tendency to fibrillation. The view that calcium is mainly concerned in stabilizing the membrane in cardiac muscle does not, however, explain why raising the calcium to 4·4 mM/l. causes fibrillation in a much larger percentage of hearts.

Of the observations so far made the effect of changes in potassium concentration are the most difficult to understand. Potassium may cause fibrillation, and also may arrest it. Thus Grumbach (1956) has shown that, after an injection of adrenaline, the injection of KCl into the fluid perfusing an isolated heart caused fibrillation. A discussion of the opposite effects of potassium on arrhythmias whether produced experimentally or occurring clinically is given by Scherf and Schott (1953).

In atrial fibrillation in the heart-lung preparation a slow infusion of KCl into the blood sufficient on the average to raise the plasma K^+ concentration from 5 to 8 mEq./l. arrested the fibrillation. Similarly, in ventricular fibrillation when the potassium concentration was doubled, fibrillation did not occur in any heart, and, on the other hand, a diminution of potassium in the perfusing fluid increased the proportion of hearts fibrillating. Now several observers have found that an increase in extracellular potassium concentration shortens the duration of the action potential (Yoshida, 1926; García Ramos and Rosenblueth, 1947, who worked on the dog auricle, and Weidmann, 1956). Weidmann's observations showed that the shortening could be obtained without preceding depolarization. Thus it seems that an increase of K^+ ions externally can hasten repolarization in some way, and if the rate of repolarization is indeed concerned with fibrillation we would expect that potassium would increase the tendency to fibrillation rather than oppose it. The amounts of potassium used by us to arrest atrial fibrillation seem to have been less than the smallest amount used by Weidmann, and it may be that the amounts necessary to arrest fibrillation have another action. Hodgkin and Keynes (1954) have shown that in *Sepia* nerve the sodium pump is depressed both by dinitrophenol and also by a low external potassium concentration. If this is true for heart muscle the effect of low potassium in inducing fibrillation and that of higher potassium in preventing it may be related to its effect on the sodium pump. Since dinitrophenol increases the tendency to fibrillation it is probable that this is because it depresses the sodium pump, and if so the antifibrillatory action of the amounts of potassium we used may be explained by an increase in the action of the sodium pump. Fortunately this can be tested experimentally.

The main results of the investigations are in the first place methods for the study of both atrial and ventricular fibrillation which are relatively simple to use; in the second place observations which indicate that an approach to fibrillation in terms of the movement of ions is likely to be very fruitful. On the whole, the attempt to explain fibrillation in terms of the factors affecting the action potential has had considerable success; indeed, what failure there has been does not suggest that the approach is wrong, but rather that through a study of fibrillation more light may be thrown on the ion movements in cardiac tissue when a normal rhythm is being maintained.

Summary

Hitherto no methods have been available for the quantitative study of factors influencing fibrillation in either the atria or the ventricles of the heart. Three methods are now described. Atrial fibrillation has been produced in the heart-lung preparation of the dog by applying brief stimulation to the atrium during the slow infusion of acetylcholine. Following this observation fibrillation has been produced in the isolated atria by stimulation in the presence of acetylcholine. Fibrillation occurs when the exchange of sodium and potassium ions reaches a certain value per unit of time.

Ventricular fibrillation has been studied in the isolated rabbit heart. When electrical stimulation at a rate of about 600 per min. is applied to the ventricles until they fibrillate, the continuance of fibrillation after the stimulation has stopped has been shown to depend on various factors. Fibrillation is more likely to continue the lower the potassium concentration of the perfusing fluid, and the higher the calcium concentration. The effect of variation in the calcium concentration is, however, triphasic. Fibrillation is more likely to continue in the presence of dinitrophenol, and on the other hand, fibrillation is arrested in the presence of adenosine triphosphate. Fibrillation is attended by an increased loss of potassium ions

from the ventricles. These and other observations represent the early stages of an investigation of the factors involved, but they already suggest that fibrillation is closely related to the rate and extent of exchange of ions across the cell membrane.

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Section of Pædiatrics

President—D. V. HUBBLE, M.D., F.R.C.P.

[*May* 24, 1957]

DISCUSSION ON THE PROBLEMS OF SPINA BIFIDA CYSTICA

Dr. D. MacCarthy and Dr. Mary Lindsay:

Spina Bifida as a Pædiatric Problem

When a child presents multiple problems it is best if he can be looked after as a whole by a pædiatrician who co-ordinates the work of the specialists. Cerebral palsy is an obvious example but spina bifida, if the child survives, requires the same sort of care; fortunately there are much fewer cases. We would like to emphasize that care of the whole child in spina bifida, as in other diseases, includes care of the parents, and even if the infant dies in the first few weeks the pædiatrician has still a responsibility.

Though we cannot here discuss the causation and pathology of spina bifida, the question of its incidence and its heredity does concern us. Reports in the literature show a considerable variation in different parts of the world. Record and McKeown (1949) showed a falling incidence in Birmingham in 158,000 births in the course of seven years. It was 3·35 per 1,000 in 1940 and 1·63 per 1,000 in 1947, the average being 2·45 per 1,000. McMahon *et al.* (1953) record 2·53 per 1,000 in Rhode Island and Harris and Steinberg (1954) 2·4 per 1,000 in Rochester, Minnesota. The highest published figure of the incidence of spina bifida in England after Birmingham 1940 is that of Malpas (1937) in Liverpool who, in 13,964 births, found an incidence of 2·8 per 1,000, i.e. approximately 1 in 350 births. A still higher figure is recorded by Coffey and Jessop (1955) in Dublin, who in 12,552 births found an incidence of spina bifida of 4·2 per 1,000, i.e. approximately 1 in 240. Professor L. S. Penrose (1957) thinks that a geographical distribution of high or low incidence is probably definable in Europe.

Inquiry into the incidence of spina bifida in Buckinghamshire shows a figure comparable to Liverpool, one of the highest recorded in England. This part of England may even be one of these areas of high incidence suggested by Professor Penrose. In the course of this inquiry we have learnt many facts about the fate of these infants and the sufferings of their families. Taking all births in our two hospital maternity units (including unbooked cases) and three general practitioner maternity units in the course of six years, there were 11,300 births and 32 cases of spina bifida, an incidence of 2·8 per 1,000. The incidence among hospital births is about 30% higher than in the general population if unbooked cases are included, as cases of spina bifida and anencephaly tend to go with complications of pregnancy and labour which lead to admission as emergencies (Penrose, 1957). 11 of our series were still-births and 21 live births. This means that a pædiatrician who sees 1,000 newborn infants a year will see between 2 and 3 live-born cases a year in maternity homes or hospitals. In addition, cases born at home will be brought to his notice and may double this number. Many pædiatricians see 2,000 or 3,000 newborn infants a year and with cases born at home will be confronted with spina bifida problems twelve times a year.

The fate of our 21 live births can be briefly told. 11 died in hospital under twenty-eight days. 6 died elsewhere between the ages of two months and two years, leaving disturbing memories in their families. They all developed hydrocephaly and parents who could not keep them at home were relieved of the burden (by various expedients) either temporarily in our hospital beds or permanently elsewhere. The remaining 4 are still alive. A boy, aged 4½, is intelligent, walks and has sphincter paralysis. A girl, aged 6, is intelligent, walks, or rather waddles, and has sphincter paralysis. A girl, aged 2, is intelligent, walks on one strong leg and one weak leg, has a very deformed back, but tight sphincters. A boy of 9 months is intelligent, has a sacral skin-covered tumour with slight neurological involvement of the lower limbs. We have also, from another county, a 4-year-old girl with a skin-covered myelomeningocele, intelligent, and complete paraplegia at D.12, incontinent, and rejected by her family from birth. She has spent all her life in a hospital and is soon going to a Barnardo home.

This group of cases is fairly representative of the conditions to be found in survivors who amount to 20% of the total. The first three had their myelomeningocele removed as newborn infants. If a policy of masterly inactivity had been adopted they might have developed meningitis and died, but more probably they would have survived as they did not develop any severe degree of hydrocephaly.

Salvage of apparently hopeless cases is now attempted in many fields with some worthwhile results. But when a child with myelomeningocele is born it is very difficult for the

parents to grasp fully what the child is in for and what they themselves are in for if it survives. The reaction of fathers very often is mentally to "write off" this child. Often the very first question he puts is, "Will the next child be all right?" But mothers who, one must remember, have known their child internally for several months feel different and instinctively wish for its survival, though occasionally they have a revulsion against it. When the parents do not feel alike about the child there is a danger to their relationship and we have seen this become serious when, as time goes on, a child becomes hydrocephalic. We have learnt from close follow-up of the children surviving for a few wretched years that mothers suffer far more over the hydrocephaly than over the raw area on the back. One cannot formulate any rules for the management of these bad cases. To adopt a policy of taking charge of the baby completely and removing it from the sight of parents to hospital, where they thrive, or to linger in quiet corners elsewhere till the end comes, would be utterly wrong for certain parents, who demand out of human feelings, or a moral or religious attitude, that the utmost be done to save their child.

The occurrence of other affected children in a family is familiar to everyone. We have met this three times in our small series. To generalize on the findings with regard to heredity of the grosser nervous system defects Penrose (1946) has shown that advanced maternal age gives an increased incidence. Polman (1951) in 105 cases of anencephaly found an incidence of 6·5% of gross nervous system abnormalities in sibs. Penrose (1957) from a similar study rates the likelihood of a second affected child at about 1 in 20 and of a third affected child 1 in 4. Malpas (1937) found in 39 fraternities containing a spina bifida, a still-birth and neonatal death-rate of 29%. Parents have a right to know these gloomy facts if they ask for them, and if they do not ask it is a matter for our private conscience whether we tell them or not. They often fear another abnormal child and wish to make the best life they can for the afflicted child.

If we are asked to salvage one of these severe cases, we and the parents ought to know about the failures as well as the successes and we should remember that even with arrested hydrocephaly individuals have a shallow cortex and may in character be shallow also. We doubt whether this Discussion will convert our pessimism about spina bifida cystica into optimism. We think it will be disquieting if it does.

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Mr. G. H. Macnab:

I shall confine my remarks to my own observations in a series of 200 cases.

Pure meningoceles, in comparison with myelomeningoceles, occur in about a ratio of 1 in 5. Cervical meningocele must be distinguished from the occipital encephalocele, the latter often having a narrow neck in relation to a small defect in the occipital bone, the sac hanging down over the cervical spine. The occipital encephalocele always contains neural tissue in its neck and the fourth ventricle may be dragged out into the sac. On the other hand, the cervical meningocele has a narrow neck and contains no neural content. Ventriculography may show some dilatation of the ventricular system, but removal of the sac does not give rise to post-operative hydrocephalus. I operate on patients with meningocele when four to six months old, after ventriculography. Pure meningoceles are always covered by skin, even though it may be thinned out, but sacs present in the sacral region and covered by skin often prove to be myelomeningoceles. This is due to the fact that many branches of the cauda equina have passed out through their intervertebral foramina above the spinal defect so that the neural content of the sac is small. Pure cases of meningocele never produce clinical evidence of paralysis, but cases of sacral myelomeningocele covered by skin may show no evidence of paralysis in the lower limbs, as the nerve supply is intact, but at a later date control over micturition and defæcation is shown to be defective. The pure meningocele always has a narrow neck to its sac and in a few cases we have evidence of a shutting-off of the neck by fibrosis, but on the other hand, on clinical examination the narrow neck may be masked by the presence of a deposit of lipomatous tissue. It follows that the diagnosis of a pure meningocele is made at operation, so I always warn the parents that my operation is exploratory in character. No guarantee of cure can be offered until the findings show a sac with a narrow neck containing cerebrospinal fluid and not more than three to four fibrils which always prove to be fibrous and not neural.

My definition of the myelomeningocele is a sac lined by the membranes surrounding the

spinal cord which contains cerebrospinal fluid. Into the sac pass the spinal cord or nerves of the cauda equina. These nerves pass to the fundus of the sac wall and form part of its wall, true epithelium is absent and ulceration is seen at birth. Within a few days granulation tissue begins to form and healing takes place by fibroblastic reaction in four to eight weeks, leaving a scarred area in the fundus of the sac. The initial appearance of ulceration suggests infection and often a poor prognosis is given but only 18% have developed meningitis in my series. The sac is often loculated due to sheets of arachnoid fusing together, so that the cerebrospinal fluid in the spinal canal is shut off from the content of the sac and thus inflammatory reaction remains localized. The greater the loculation in the sac the greater is the neural content.

In 50% of cases that have come to post-mortem there have been pathological changes in the spinal cord proximal to the sac, mainly in the form of hydromyelia, and Dr. A. H. Cameron has shown that myelinization of the tracts has been retarded. These pathological changes in the cord account for the curious distribution of the paralysis in the lower limbs, e.g. a flaccid limb with movements present in toes, or a return of a degree of motor power to a limb that appeared completely flaccid at birth. The clinical appearance of the sac with its poorly-formed skin covering suggests the diagnosis of a myelomeningocele and the presence of paralysis confirms it, but 21% of my cases show a membranous covering with no paralysis and those in the sacral region show a skin covering with no paralysis in the lower limbs, though the bladder is usually involved.

Myelomeningoceles without clinical evidence of paralysis form a small but important group for they can be de-capped and the neural content replaced into the spinal canal and fascial flaps brought over the spinal defect. The timing of this operation is dependent on the fact that 47% of my cases of myelomeningocele developed progressive hydrocephalus within the first eight months of life due to the presence of an Arnold-Chiari malformation. The onset of hydrocephalus may be slow, or even arrest in a few cases, so the de-capping operation for myelomeningocele is not carried out under eight months. An Arnold-Chiari malformation varies in size but does not act as a plug to the foramen magnum and cervical canal. In these cases there is usually a communication of cerebrospinal fluid between ventricle and spinal canal. The cause of slow development of hydrocephalus appears to be venous congestion over the deformity, setting up arachnoiditis and blocking of the sub-arachnoid space.

Fate of the Child with a Myelomeningocele—the Early Case

Hydrocephalus.—46 cases showed evidence of hydrocephalus at birth, and 23 cases showed onset of hydrocephalus between the second and eighth month of life. Ten cases were kept under observation for one year before I could satisfy myself that progressive hydrocephalus was not present. Rapid progressive hydrocephalus with raised ventricular pressure over 250 mm. occurring in the first three months will lead to death within one year. Slow onset with low pressure may arrest. If ventricular and spinal dye absorption is high, there is a communicating hydrocephalus with a proportionate degree of absorptive surface. I carry out a subdural dye absorption study and if the result is over 50% I connect the ventricle with the subdural space by the use of a plastic disc.

Meningitis.—The clinical state of so-called ulceration seen in the first week of life would suggest that meningitis was inevitable in all cases. An analysis of 150 cases showed 23 with large thin membranous ulcerated sacs that did not develop meningitis during their life. 28 with ulceration developed meningitis during conservative treatment, and 15 with severe ulceration developed dense fibrosis without meningitis so that healing of the sac took place without operation. The remaining cases had a mild degree of ulceration that healed in a period of four to eight weeks. If I see a thin membranous ulcerated sac I cover it with skin flaps if the size of the spinal defect permits.

Leaking of the sac.—53 cases out of the 150 developed a leakage of cerebrospinal fluid within the first six months, and 30 cases survived. The high survival rate from rupture of the sac is largely due to loculation of the sac shutting it off from full communication with the spinal canal.

Fate of the Child with a Myelomeningocele—the late Case

Incontinence of urine.—This type of paralysis is such that the urine dribbles away continuously, so back-pressure does not occur. Acquired hydronephrosis is a late development, and urinary infection is usually low-grade as there is no stagnation, and can be kept under control with the use of sulphonamides or antibiotics for many years. Trophic ulceration around the vulva in the female with secondary infection is a severe complication, and in my cases I have had to resort to diversion of the urinary stream by uretero-ileal anastomosis. Where motor paralysis in lower limbs is slight or non-existent the psychological problem of the wet, smelly child at normal school arises about the age of 8 years. If, after the first year of life, you can cause dribbling of urine by pressure on the bladder, no form of conservative treatment will give satisfactory control in later life.

Incontinence of fæces.—It is interesting to note how these children can gain a measure of control with poor sphincter tone. They form a plug of fæces which blocks the anal canal. The child soon finds the correct diet and fluid intake to produce a mild constipating effect. In such a case ureters cannot be transplanted into the colon to control incontinence of urine. In severe cases I carry out colostomy in the adolescent.

Trophic ulceration occurs around the vulva and anal canal in association with incontinence. A period of in-patient treatment will often clear up the anal ulcers, but where urinary incontinence is severe the stream has to be diverted. Trophic ulceration on the dorsum of the foot or toes, due to pressure by shoes, may respond to conservative measures, and sympathectomy is of great value if the response is poor, but where ulceration occurs on a weight-bearing surface like the heel it usually ends in amputation. In such cases the motor paralysis is usually slight and sensory loss confined below the level of the knee-joint so that amputation can be carried out.

Motor paralysis.—Most infants retain some power in the quadriceps, so that contractions suggest to the mother that the whole leg moves. A fair proportion of those children who survive beyond the age of two years have sufficient tone to stabilize the knee-joint, so that boots and calipers may give them locomotion. These children have never walked and their chief difficulty is learning to walk is flexion contractures at the hip-joints set up by pain on attempted movement. De-capping of the myelomeningocele, covering of spinal defect with fascia, and closure of wound with healthy skin relieves pain on movement and allows the hip-joints to be extended. Attempted walking is greatly assisted at this stage by the supply of stiff leather boots with uppers to mid-calf, and without toe-caps. These boots keep the feet at right-angles to the tibiæ where the paralysis is greatest and give a firm base for weight-bearing.

SUMMARY.—Pure meningoceles only form a small percentage of cases of spina bifida cystica. Their removal results in a normal child. There is also a small group of myelomeningoceles without clinical evidence of paralysis that can be restored to normality by de-capping. Early onset of hydrocephalus will lead to a rapid death and 47% of cases of myelomeningocele are associated with hydrocephalus. The complications of meningitis and leakage of cerebrospinal fluid from myelomeningoceles account for 26% of deaths. In the late cases, incontinence of fæces is more easily controlled than that of urine. Trophic ulceration in relation to a toe will usually heal with rest or rest and sympathectomy. Trophic ulceration on a weight-bearing surface usually leads to amputation. If motor paralysis is confined to below the level of the knee-joint walking with the aid of instruments will usually be possible provided that the myelomeningocele has been de-capped allowing extension of the hip-joints.

Mr. D. F. Ellison Nash:

The Management of Fæcal and Urinary Incontinence and the Associated Hazards

There are two distinct, but nevertheless, related clinical problems. The first is that of the neglected case which requires full investigation, assessment and probably a good deal of salvage work before one can set about an effective rehabilitation programme. The second is that of the management of the sphincter deficiency from birth, and the prevention of retention damage.

The first group has really been the basis of my personal experience. Most children have come between the ages of 5 and 10 years without previous urological investigation. A considerable number already had advanced renal disease. In addition, many of the children had gross orthopædic deformities, penetrating ulcers, a severe educational deficit and a background of dismay and depression. Our urological programme has always had to be fitted into the general plan of management of the other complications.

Considerable variation in sphincter and viscus involvement, both on the motor and sensory side, is produced by growth of the child, by change of posture, by increased activity and by the development of the prostate and uterus at puberty.

Whichever group we are considering—the neglected late case, or the neonate—it is necessary to see clearly our ultimate goal. It is not only survival, but a full education, leading to employment and a satisfactory social life. Though in many cases we cannot hold out hope that there will be a normal adult life, one knows both men and women who have so overcome their total disability, even with amputation, that they can go swimming, or enjoy an adequate game of squash, in spite of unreliable sphincters.

Bowel control.—Even in those who seem to have a fairly good anal sphincter mechanism, there is a variable lack of rectal sensation. This leads to constipation and to the development of a megacolon which requires rehabilitation by regular enemas, neostigmine and training.

Those children who have a patulous anus, similarly lack sensation. There is therefore no spontaneous evacuation of the rectum. The initial task is to remove the inspissated faeces by various means—manual evacuation, judicious enemas using bile, or manoxyl as a solvent. Subsequently the general principles of management are those of a colostomy.

Some children can be trained to regular evacuation by the use of a glycerin suppository if the anus is tight enough to keep the suppository in position. A warning must be given about manual evacuation and enemas since it is possible to injure the insensitive rectum and produce a pelvic abscess, or peritonitis. Fæcal incontinence is not inevitable, and training leads to the stage when there is nothing more than a slight stain on the underclothes at the end of a strenuous day.

Micturition.—The management of micturition is concerned with two things; retention, with pressure damage on the kidneys and infection, and urinary incontinence. The normal, automatic bladder of the baby prevents our assessing whether the bladder is distended, or whether there is residual urine. You must know—"is the urine leaking out *all* the time?" or "does it come in squirts with dry intervals of even a minute?" If there is no residual and the urine is clear, excretion pyelography can be postponed until nine months or a year. If the bladder is distended or if there *is* residual urine, then full urological and instrumental investigation is imperative. If the bladder is being emptied continuously or intermittently the infant should be "pot" trained at set times with increasing intervals to educate what may remain of the neuro-muscular mechanism.

After an adequate period of observation and full urological investigation, the cases may be separated into one of three main groups. It must, however, be emphasized that the intellectual and physical capacity is of paramount importance in planning the treatment. (Table I).

TABLE I.—URINARY INCONTINENCE: CLINICAL CLASSIFICATION

Group 1.	Complete incontinence *without* residual urine.
Group 2.	Continuous or intermittent incontinence *with* residual urine.
	(*a*) without sacculation or upper tract dilatation.
	(*b*) with sacculation and/or upper tract dilatation.
Group 3.	Retention with overflow incontinence.
	(*a*) without back pressure structural change.
	(*b*) with back pressure structural change.

Group 1: A continuous leak, or an automatic bladder with no appreciable residual urine. This is the state of affairs found in the normal newborn baby. Many spina bifida babies have this relatively normal bladder behaviour when born, and only develop complications as the months pass, possibly from superadded infection. The treatment of this group is the control of infection, if it arises, and careful observation for deterioration.

Group 2: Incontinence *with* residual urine. The obstruction must be relieved. In the boy this is done by transurethral bladder-neck resection, and this may be adequate to allow normal control to develop. A moderate amount of sacculation in the urinary tract does not seem to matter once the obstruction has been relieved. If diverticulum formation is severe, or if the ureters have become grossly dilated and rigid, the relief of the obstruction must be really radical and undoubtedly in some of these patients the immediate diversion of the urine from the bladder to an isolated ileal loop is preferable. A number of patients with only a moderate amount of residual urine may overcome their disability by regular manual expression of the bladder, but if they *are* able to express the bladder satisfactorily, it is likely that they have stress incontinence when the bladder is only moderately full. If infection persists in the presence of residual urine a diversion operation is necessary.

Group 3: This represents the really dangerous group—those with retention-overflow, and in all probability, irreversible pyelonephritis.

This broad basis serves as a guide in planning treatment, details of which have already been published (Nash, 1956*a*, *b*, 1957).

First, there is time training. In this the mother needs to find out how long the child can go without leaking, and she then trains the child to micturate by straining at set times. With an intelligent mother and a co-operative child complete control may be obtained and strict time training forms an essential part of management even in those who have had various operations.

The second aid is manual expression and this is necessary if there is resistance at the bladder-neck due to alteration of angle, or simple muscle inco-ordination.

If manual expression is not possible retention is relieved by resection of the bladder-neck. This is a difficult procedure performed with a miniature resectoscope. All those patients who have a residual urine of more than 60 ml. after manual expression require resection to allow manual expression to be effective. In boys, overdoing the resection produces continuous incontinence necessitating the use of a urinal and if the resection is insufficient the obstruction recurs as the prostate grows. In girls, resection frequently leads to a vesico-vaginal fistula.

Urethral plication was originally devised for the treatment of post-prostatectomy incontinence. It consists of the insertion of supporting and partially compressing mattress

sutures of silk or nylon between the ischiocavernosus muscles in the perineum. The bulbocavernosus muscle is frequently atrophic and sometimes completely absent. The cases particularly suitable are those boys who have some degree of control. It is an operation with very little risk and tremendous dividends; in my hands it has failed several times, but in five out of twelve it was completely successful. It can be used after bladder-neck resection to restore control in certain cases.

Pudendal neurectomy.—I have very little experience of it. I have used it once to reduce very severe priapism which was preventing manual expression and use of a urinal.

Urinals.—No effective urinal has been devised for the girl, and an indwelling catheter is thoroughly undesirable. For boys with no appreciable residual urine, modern plastic lightweight urinals are worth a trial, but in many cases something more is needed. One of the main difficulties is that wearing a urinal night and day leads to a cauliflower-like penis, risk of meatal stenosis and urethral fistula.

Ileo-cutaneous ureterostomy.—The complete diversion of urine from the bladder by means of an isolated ileal loop—i.e. an ileo-cutaneous ureterostomy—is an operation which has come to stay. It is a major operation which carries a little risk, but a major reward. It is an irreversible procedure to be undertaken only when it is clear that the degree of incontinence or damage to the urinary tract is such that the patient will be unable to enjoy a full education, profitable employment or a moderately happy social life (Table II).

TABLE II.—ILEO-CUTANEOUS URETEROSTOMY

Conversions from suprapubic cystostomy (renal failure)	7
For vesico-vaginal fistula	3
For infection and incontinence	2
Total	12

Male—2.
Female—10.
Operative deaths—nil.
Subsequent deaths—2 (1 renal: 1 unconnected).
Selected cases awaiting operation—4.
Operation indicated in 16 cases out of 78 observed=20·5%.

The dramatic change in the general health of those children who have been submitted to this radical operation has been almost unbelievable.

In boys, bladder-neck resection, and wearing a penile urinal is appropriate treatment for the majority; those who exhibit back-pressure would probably do better with a diversion operation. In girls, bladder-neck resection should be tried when training and manual expression have failed, but it seems likely that an ileo-cutaneous ureterostomy is the ultimate treatment of choice.

There is no place in my opinion for suprapubic cystostomy, penile clamps or sling operations.

If we take a long-term view we are now in a position to say that urinary or fæcal incontinence must not be accepted as a barrier to the child's intellectual, occupational and social progress; we might fairly speak of spina bifida "*sicca*".

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Dr. L. Guttmann [*Summary*]:

The remarkable results achieved in recent years, in the treatment and rehabilitation of traumatic paraplegics, have had their effect on our approach to the management of other forms of spinal paraplegia. No longer is it a question of whether the majority of spinal paraplegics can be returned to useful life but how soon.

In this paper, something is said about the plight of patients with spina bifida who have survived for many years, and complications are discussed which could have been avoided with adequate management from the beginning. It is impossible to cover here the whole ground of this complex problem, and only a few of the pertinent points are mentioned, which have emerged from observation on 40 patients with spina bifida, studied at the National Spinal Injuries Centre, Stoke Mandeville.

Over 50% of the total material reached adolescence, the eldest patient being 41 years old. In most of the patients, the symptoms of paralysis were discovered either immediately following birth or shortly afterwards. In only a few cases did the symptoms develop later and one man with retained myelomeningocele developed a transverse spinal syndrome at the age of 22—below T.11 on the right and L.1 on the left—shortly after his "Dodgem" car bumped into another car at a fair and he was hit at the site of the myelomeningocele.

Skeletal Abnormalities Due to Mal-development and Muscular Contractures

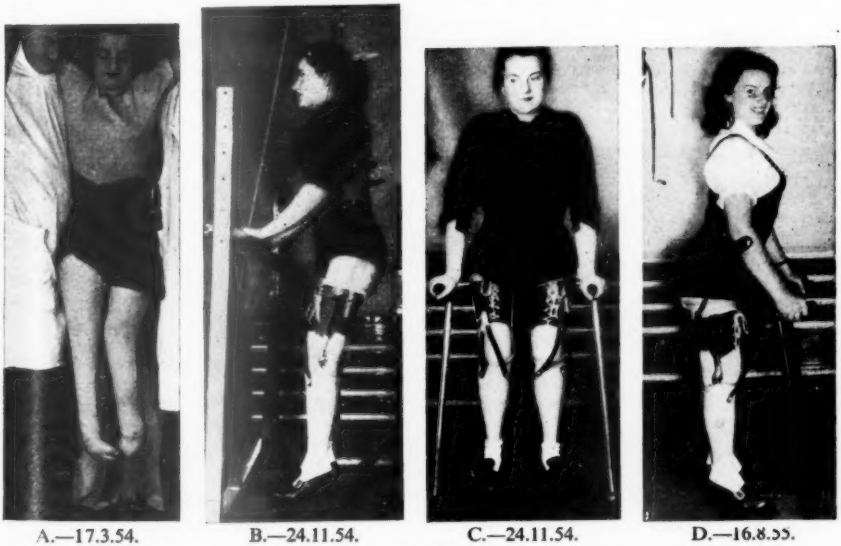
In analysing the skeletal abnormalities found in these patients, one has to distinguish between those due to mal-development of the spine and other parts of the skeletal system and those which develop later, as a result of inadequate management of the patient. Neglect of either may have serious consequences for the later activities and health of the patient. Special attention is drawn to the equinovarus deformity of the feet. If overlooked or neglected in the early stages following birth, this deformity may take grotesque forms and contractures result, which make standing and walking impossible, although the neurological lesion may be only that of a distal cauda equina lesion—say below L.4—where the quadriceps and gluteus maximus are intact. This deformity of the feet is frequently combined with a postural deformity of the pelvis and lumbar spine, due to prolonged positioning of the pelvis in hip flexion. This leads to contracture of the iliopsoas and quadratus lumborum, especially in lesions below L.1, where these muscles are more or less intact, while their antagonists are paralyzed. The result of the contractures of these muscles is a hyper-lordosis with backwards distortion of the pelvis. The following case is a good example:

Case I.—Girl, aged 17. Spina bifida, partial paralysis both legs, talipes equinovarus; several unsuccessful operations to correct deformity. Never able to stand though quadriceps and glutei good both legs. Gradually developed hyper-lordosis and backwards distortion of pelvis through constant sitting in bed or chairs (*see* Fig. 1).

On admission.—Complete cauda equina syndrome below L.4. Having regard to the uselessness of the feet, on the one hand, and the good quadriceps and gluteus maximus function on the other, I felt that below-knee amputation and the provision of artificial legs might enable this girl to stand and walk. Amputation carried out (Mr. Geoffrey Platt).

Iliopsoas contractures and spine and pelvis deformities gradually overcome by hanging in harness (Fig. 1). Aged 18, patient able to walk with elbow crutches. Subsequently, with bladder training, correlating intake of fluid with regular voiding, she became absolutely dry.

Readmission follow-up: walking on elbow crutches improved, health very good, urine sterile, regular function of both bladder and bowels, now employed in a factory.



A.—17.3.54. B.—24.11.54. C.—24.11.54. D.—16.8.55.

FIG. 1.

Skeletal Deformities Due to Pressure Sores

Another skeletal deformity, as a result of inadequate management, which may cause most serious consequences, is osteomyelitis, as a result of neglected pressure sores. This complication develops particularly over the trochanteric and ischial areas but may also develop over the ankles and sole of the feet. The infection may penetrate into the deeper tissues and involve, if not checked, the ischial ramus, spreading into the hip-joint, which eventually completely disintegrates (Guttmann, 1954, 1955).

Such serious complications can definitely be avoided, if proper precautions are taken from the beginning. The most important of these is prevention of pressure, at all costs—in particular, by not allowing the patient to sit, once a sore has developed, until it is soundly healed.

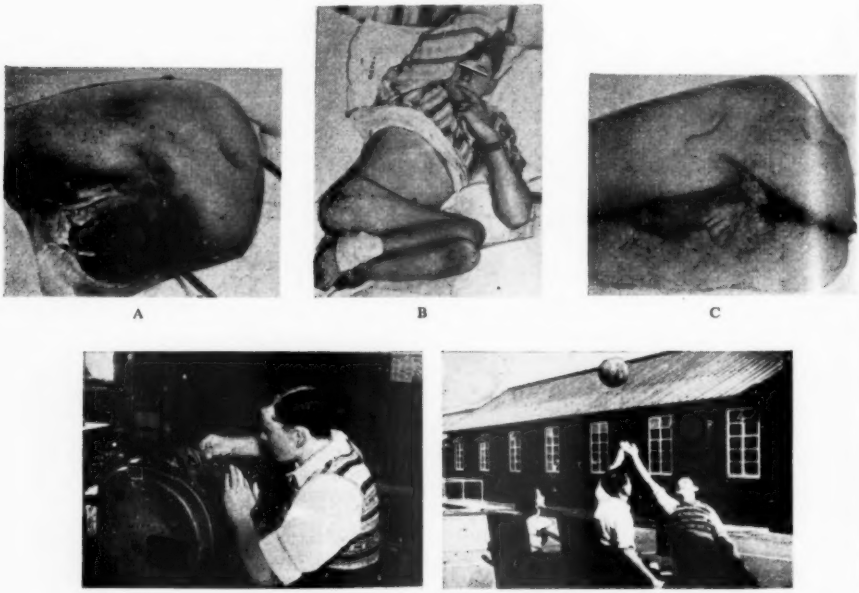
However, the best cure for pressure sores in spina bifida, as in other forms of paraplegia, is prevention, and both the patient and his attendants have to be well instructed about the mechanism of formation of sores and the factors promoting them (Guttmann, 1956).

Bladder Paralysis

The value of detailed examination by cystometrogram, cystogram and intravenous pyelogram cannot be overstressed in these patients. These investigations are invaluable for the differential diagnosis between the abnormalities of the urinary system, caused by neurological lesion and infection, on the one hand, and congenital abnormalities of the renal system, associated with spina bifida, on the other. In this connexion, attention may be drawn to the fact that vesical incontinence, which is one of the most predominant clinical symptoms in these patients, may not always be due to paralysis of internal and external sphincters but to overflow, as occurs in paraplegics from other causes. Training the patient, by correlating his fluid intake and output by going to the toilet at regular intervals, which are gradually increased, can be very successful indeed (*see* Case I). It is true that this training is particularly difficult in children with low intelligence or lack of concentration, but, with great patience on the part of the attendants in hospital, institution or at home, encouraging results can be achieved.

Various methods of artificial drainage have been introduced to combat retention and incontinence. Of all the methods used, the most unsatisfactory is the perineal urethrostomy. The disastrous effects resulting from this method are best illustrated in the following case:

Case II.—Patient, now 23, with an incomplete cauda equina syndrome below L.2, following a spina bifida and myelomeningocele, suffering from urinary incontinence, had a perineal urethrostomy done at the age of 17. He very soon developed a sore in the perineal area, which never healed and gradually worsened. He was admitted in a most pitiful condition and, in addition to profound contractures in hips and knees and deformities of feet, he had a large pressure sore, involving the whole perineal area (Fig. 2) and penetrating into the urethra. He was highly septic, with a hæmoglobin of 62%. However, we succeeded in obtaining healing of the sore and fistula. Following circumcision, the frontal part of the urethra was gradually dilated and a catheter passed. Eventually, the urethral fistula was closed by plastic operation and the patient trained in self-catheterization. Fig. 2 also shows the later stages of this patient's successful rehabilitation.



A B C

D E

FIG. 2.

In many spina bifida patients with incontinence, the wearing of a rubber urinal is necessary, to make them socially acceptable. The patient must be thoroughly instructed in the proper wearing of rubber urinals and informed of the risks involved in producing pressure over the posterior surface of the penis.

Care of the Bowels

Incontinence of the bowels in spina bifida patients is easier to combat than urinary incontinence. Rectal incontinence may be due to overflow from overloading of the colon, as the result of chronic constipation. The aim is to develop, in these patients, as is done in other paraplegics, a habit of regular emptying of the bowels, which eventually makes them socially acceptable. Colostomy should be reserved for very selected cases only.

Finally, the importance of systematic education, training, regular work, and employment must be emphasized for the social integration of spina bifida patients. The defeatist attitude of the past, on the part of the medical profession, as well as the public as a whole, is unjustified in many of these patients, and a more optimistic and dynamic approach towards these unfortunate people is imperative. It has been proved that many of them can eventually master their disability and be gainfully employed, in one way or another, and several of the patients of this Centre are now employed in full-time factory work.

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Dr. K. M. Laurence:

Hydrocephalus developing in cases of cystic spina bifida can satisfactorily be accounted for by co-existent intracranial malformations or the occurrence of ascending infection. Early surgery may prevent the latter, and a brief survey of 183 unselected cases at the Hospital for Sick Children, Great Ormond Street, suggests in fact a much lower incidence of hydrocephalus in operated cases (40%) than in those treated conservatively (75%). The operation of choice would appear to be deflation of the sac and covering by skin flaps rather than radical excision, as this avoids the risk of damage to the spinal cord.

Mr. A. N. Guthkelch:

The essentials of the management of a case of spina bifida cystica in infancy are to preserve the maximum of neurological function and, if possible, to diminish the risk of hydrocephalus. It is important to enquire whether the timing of the operation upon a case of myelomeningocele can affect either of these.

As to the eventual degree of neurological deficit one might have thought that operation in the neonatal period would prevent any tendency to infection in the exposed cord, and therefore to ascending myelitis with a consequent further loss of neurones, but the results in a personal series of cases have not really fulfilled expectation. As to hydrocephalus, since local infection of the sac sometimes leads to a more generalized involvement of the meninges, and since bacterial meningitis is one of the commonest causes of infantile hydrocephalus, one might suppose that early closure of a myelomeningocele would be helpful in preventing this. Of course, however early one operates the area granulosa is always contaminated, and from time to time a flare-up of infection (and therefore increased intracranial pressure) in the post-operative period must be anticipated—this may have been the origin of the belief, now generally abandoned, that removal of the sac in itself precipitates hydrocephalus. But I have the impression from a group of recent cases too small to be statistically significant that operation in the neonatal period decreases the risk rather than the reverse.

None the less the state of any child with both paraplegia and progressive hydrocephalus is so pitiable that everyone will sympathize with the instinct to postpone repair of the spina bifida until is is fairly clear that the head is not enlarging unduly, and it is certain that no particular timing of the operative procedures is applicable to all cases. Each must be judged as a separate problem.

Finally, we should not forget the possible risks of operation. In a series of over 300 cases I have found the direct operative mortality negligible. In 3 cases the child's neurological deficit was significantly increased by operation, doubtless because in a chronically infected case the identification and preservation of all functioning neural tissue may be very difficult, but the deterioration was never catastrophic. We might reasonably conclude that the benefits of operation outweigh the risks.

Mr. C. H. Macnab (in reply to Mr. Guthkelch):

The venous congestion over the Arnold-Chiari malformation setting up a closure of the subarachnoid space is only one form of cause of the development of hydrocephalus where a myelomeningocele is present. I put it forward as an explanation of the slow development of hydrocephalus, the ventricular pressure usually being low, as there is not a congenital intraventricular block. With regard to the question of early closure of the defect set up by a myelomeningocele to prevent the onset of meningitis or leaking of the sac, I find it is

only in a small proportion of cases that the skin coverage is adequate, and unless you can close the defect in the spine with fascia there is no guarantee that you will avoid leakage of cerebrospinal fluid. As 47% of cases of myelomeningocele develop hydrocephalus within the first eight months of life I do not carry out the early operation unless the defect is a small one and the covering is so thin that leakage and meningitis are imminent.

With regard to the question of active treatment or no treatment, the point I would stress is that these children should not be abandoned by the medical practitioner. It is my experience that when the child is born with the defect the parents often wish it to be removed by the State, but later on they come to enjoy the presence of the child and gain solace by the devoted care they can give to the infant. During this period they must always have the backing of the medical practitioner and specialists so that a little hope for the future can be given to them. The ideal is to encourage the parents to look after the infant and only admit to hospital or institution when the child gets beyond the management of home nursing, or where a definite programme of active specialised treatment is to be carried out.

Dr. Hugh Jolly (*summing up*)**:**

Those who have taken part in this Discussion have shown that they all feel the same uncertainty as to the correct treatment for children with spina bifida and have raised the question when, if ever, they should withhold treatment. Dr. MacCarthy's figures illustrate the frequency of the condition which is indeed a challenge to all of us and can only be tackled by team work. They were obviously depressed by the problem and this depression, which must be common to most paediatricians, was in contrast to the enthusiasm of the surgeons who are tackling the problem. Admittedly, many of the infants we see die before reaching the surgeons and we have had to cope with the emotional problems surrounding their life. At the same time it is obvious that we must be influenced by the fact that the surgeons feel they can do much to help these children.

Dr. MacCarthy emphasized the rift which could so easily develop between the father who was prepared to "write off" the child and the mother, who, with her normal maternal instincts, could never bring herself to think in this way. Mr. Macnab's figures drew attention to the much greater frequency of the meningomyelocele as compared with the meningocele and I am sure that we have all been guilty of diagnosing a meningomyelocele as a meningocele. His statement that the meningocele is always covered by intact skin is a useful diagnostic aid.

Turning to the correct time for operative treatment, it was agreed that the meningocele should be tackled between four to six weeks of age but there was a difference of opinion with regard to the meningomyelocele. In general, Mr. Macnab would leave this until the age of 8 months in order to avoid those who were going to develop hydrocephalus. Mr. Guthkelch felt that earlier operation in cases without gross neurological defect had the advantage of preventing recurrent infection of the sac, even though a flare-up of infection in the post-operative period might precipitate a hydrocephalic episode. It was agreed that the development of hydrocephalus was unrelated to surgery and occurred in about 50% of cases, except in so far as Dr. Laurence's figures suggested that removal of the sac diminished the risk of recurrent infection. The important question as to whether surgery might increase the degree of paralysis of the legs and sphincters was answered by Mr. Guthkelch who showed that such a risk did exist and had occurred in three of his cases. He believed that one should not be influenced against surgery because of it. The frequency of meningitis as a complication was only 18% in Mr. Macnab's large series.

Mr. Nash showed that many of these children could be helped by time training and manual expression and if these methods failed it was essential to determine whether residual urine was present. If this was the case the help of a urologist was essential. His term "spina bifida sicca" as the natural outcome of surgery should encourage us all to do our utmost for those who survive but have urinary incontinence.

Dr. Guttmann showed how much could be achieved by modern methods of rehabilitation and his photographs were most impressive. His figures showing the frequency with which these patients could be employed emphasize that we should not adopt an attitude of hopelessness.

The President asked the searching question as to what we know of the prognosis for these children, and of course at the moment the answer is that we have a very incomplete idea as to their future. Possibly one result of this meeting might be to set in motion some form of machinery to correlate the figures from all over the country, particularly in order to determine the place for surgery. At the same time I would agree with Mr. Macnab that the parents of a child who has been treated surgically are immediately helped emotionally, whatever the result of the treatment.

This meeting has strongly emphasized the value of bringing together paediatricians and those who have to deal with the results in adult life of problems we have to treat in childhood.

Section of Odontology

President—J. A. S. WRIGHT, A.F.C., F.D.S. R.C.S.Eng., H.D.D., F.D.S. R.C.S.Ed.

[*October* 22, 1956]

A Hundred Years of Dentistry

PRESIDENT'S ADDRESS

By J. A. S. WRIGHT, A.F.C., F.D.S. R.C.S.Eng., H.D.D., F.D.S. R.C.S.Ed.

DURING the forthcoming session we will be celebrating the centenary of the Odontological Society, as well as the jubilee of the Royal Society of Medicine of which it was a foundation society.

This is, perhaps, an occasion upon which I may be forgiven for referring to my own special and personal interest in the Section. The practice which I joined in 1923 was started in 1840 by Sir John Tomes, secretary of the Odontological Society of London at its foundation in 1856. He became President in 1862 and for the second time in 1875.

He was succeeded in the practice by his son, Sir Charles Tomes who was President of the Society in 1887. He was followed by Mr. E. G. Betts (President 1905) and then by Sir Harry Baldwin and Mr. Carl Schelling. Baldwin was secretary in 1896 and President in 1915. Schelling was secretary in 1904–5 in the years during which the negotiations were taking place which led to the amalgamation with the other societies to form the Royal Society of Medicine in 1907. He was President of this Section in 1930 and I had the honour to be one of the Honorary Secretaries during his year of office. On his retirement he presented the Presidential badge to the Section.

Prior to 1856 there was no organized professional education for dentists. The only method of obtaining any training was by apprenticeship to a private practitioner. There was, of course, no Dentists Register and clinical instruction was limited to occasional visits to the master's surgery. The pupil might, indeed, gain a good knowledge of dental mechanics, but unless he obtained a medical qualification his chance of having any training in dental anatomy or surgery was remote.

There were a few books available, notably John Hunter's "Natural History of the Teeth" (1771); "The Anatomy, Physiology and Diseases of the Teeth", by Thomas Bell (1829); and in 1847 was published John Tomes's "Dental Physiology and Surgery". Lectures on Dental Surgery were given at Guy's by Joseph Fox in 1799 and by Thomas Bell, who succeeded him.

In 1855 and 1856 two separate efforts were being made to organize dentistry upon a scientific and professional basis. On August 25, 1855, a letter from Samuel Lee Rymer, a 22-year-old dentist, practising in Croydon, was published in the *Lancet*, calling attention to the need for proper dental education and suggesting that the College of Surgeons might examine candidates who might well be termed Licentiates in Dental Surgery, and further suggesting the formation of a Dental College. This letter was favourably received by a large number of the profession, but a small group of perhaps the more eminent dentists, most of whom were Members or Fellows of the Royal College of Surgeons, or Fellows of the Royal Society, were quietly making approaches to the Royal College of Surgeons.

In December 1855 they met privately, and eighteen practitioners signed a "memorial" to the College of Surgeons, suggesting that a course of education should be held, and an examination in dental surgery instituted. This did not produce any immediate result, and while the paper was lying at the Royal College of Surgeons the memorialists agreed to constitute themselves a scientific society. A notice appeared from Rymer in the public press calling a second meeting of the profession on Tuesday, November 11, 1856, and the profession was then made aware that on the previous day (November 10) the Odontological Society of London had been formed, its by-laws framed and invitations sent to those members of the profession who were known personally to the memorialists and were deemed anxious to promote the well-being of the Society. The first ordinary meeting of the Odontological Society was held on Monday, January 5, 1857, under the presidency of Mr. Samuel Cartwright. It may be noted that he was not a Member of the Royal College of Surgeons, but was, in fact, a Fellow of the Royal Society. In the following year the Society acquired No. 32, Soho Square, and there established the first dental hospital and school, and, indeed, provided most of its staff from among the members of the Committee.

There was, unfortunately, considerable irritation in the profession generally at the

manner in which the Society had been started. A large number of highly respectable practitioners felt that the promoters had been both selfish and unjust in instituting the society in a private and clandestine manner.

The rival parties continued to work independently, and in 1857 the College of Dentists was formed, largely as a result of Rymer's campaign. Lecturers were appointed and commenced on February 18. This College opened the Metropolitan School of Dental Science in 1859, and two years later the National Dental Hospital of London. Students were examined and the successful candidates were entitled to use the letters M.C.D.E., Member of the College of Dentists of England.

The promoters of the College of Dentists were endeavouring to build up a dental profession which would be independent of medicine or surgery, while the memorialists were working to the same end through the College of Surgeons. The antagonism between the two was bitter and undisguised.

The year 1856 also saw the appearance of a monthly professional journal—the *British Journal of Dental Science*. In its opening number (July) the Editor assured his readers that its columns were open for free discussion, and at the disposal of any and every member of the profession requiring a medium for the extension of accumulated knowledge. The number for September 1856 warmly supported Rymer's plan, and there was already discussion on the title to be used by dentists, the editor feeling that it was an error, even for those who were members of the Royal College of Surgeons to call themselves Surgeon Dentists. By the end of 1856 the ownership of the *Journal* changed hands. It was offered to the committee under Mr. Rymer, which offer was refused, and then became the property of some gentlemen in the profession who supported the Odontological Society. From being the friend of the College of Dentists it became its foe and was apparently unwilling to publish its proceedings. Undaunted, the College decided to publish its own proceedings and in April 1857 appeared the first number of the *Quarterly Journal of Dental Science*.

In 1857 efforts were being made to bring about a fusion of the College of Dentists and the Odontological Society. These were unsuccessful, mainly as a result of unwillingness on the part of members of the College to follow the lead of its more far-sighted President and officers. Most of the latter resigned, and from then on the College appears to have diminished in numbers and importance, while the Odontological Society increased. The Royal College of Surgeons obtained its Dental Charter in 1859 authorizing examinations in Dental Surgery and the issue of certificates of fitness to practise. The first examination for the Licence in Dental Surgery was held by the College of Surgeons on March 13, 14, and 20, 1860, when 43 gentlemen, most of whom were distinguished members of the profession, were candidates. Among them were Samuel Cartwright, John Tomes, Thomas Bell, and Arnold Rogers, the last three being the dental members of the first Board of Examiners in Dental Surgery. They are reported in *The Times* of March 15, 1860, as "having undergone the necessary examinations", although by whom they were examined I have been unable to ascertain. In 1871 the status of the profession was further improved when the council of the College agreed to give its certificate the form of a diploma bearing the College arms and signed by the President.

In 1862 Rymer appreciated the fact that the Dental College was not going to succeed in getting a charter and so establish on a firm basis, either itself or its examination and diploma, especially as the Royal College of Surgeons had by then been empowered to admit dentists to examination and licence. He therefore approached the Odontological Society with a view to making another attempt at amalgamation.

When the first approach was made in 1857, the proposals came mainly from the Odontological Society, and, although agreed by the officers of the College, were rejected by its members. It was therefore considered desirable that the College of Dentists should, this time, formulate the proposals. On December 22, 1862, representatives of the College met Arnold Rogers, Samuel Cartwright and John Tomes for the Odontological Society, and agreed upon terms for the embodiment of the members of the College of Dentists with the members of the Odontological Society of London, under the new name of the Odontological Society of Great Britain. The amalgamation of the two bodies took place at a meeting of the Odontological Society held on May 4, 1863.

Even at this period dentists were concerned about status. The College of Surgeons had instituted in 1843, a Fellowship which carried with it a share of the responsibility for the control of its affairs. It was feared that the Licentiates in Dental Surgery might also expect a voice in the affairs of the College, but the memorialists denied any such intention. Tomes considered that education for the diploma should be equal in degree to, but different in kind from that for the Membership of the Royal College of Surgeons and may even have visualized a Fellowship in Dental Surgery.

The examination and licence in Dental Surgery were permissive and there was still no register, or limitation of the right to practise. The Medical Register was started in 1858,

but the General Medical Council refused to register the L.D.S. and this refusal was an important factor in the starting of a campaign in 1870 by Charles Fox for compulsory education and registration. This led to the election of the Dental Reform Committee in 1875 and to the passing of the Dentists Act of 1878. John Tomes was the first to inscribe his name on the Dental Register and in 1879 the Dental Reform Committee resolved itself into the Representative Board of the British Dental Association.

It is interesting to see that, in 1876, during this period of agitation for the formation of a Dentists Register the Association of Legally Qualified Dental Surgeons was formed under the chairmanship of Samuel Cartwright, Junior, with his nephew, Samuel Hamilton Cartwright, as Secretary. It appears to have been limited to Members of the Royal College of Surgeons. Both John and Charles Tomes refused to join, and it petered out after a few years. In 1900 its funds were handed over to the Royal College of Surgeons to be administered for the Cartwright Prize, and, to quote Dr. Lilian Lindsay, "as a Parthian shot from its founders, this can only be competed for by a member of one of the Colleges of Surgeons".

We must not overlook the developments which were taking place on the scientific side, as distinct from what might be called the administrative or even the political side of the profession.

It was not long before this period—in fact in 1844—that Horace Wells, an American dentist, showed that teeth could be extracted painlessly after the inhalation of nitrous oxide. A committee was appointed by the Society in conjunction with the Dental Hospital to investigate its merits and a careful report was issued based on 1,380 cases.

In 1846 Dr. Morton, a dentist of Boston, U.S.A., gave ether as an anæsthetic. Tomes took this up at once and used ether in the out-patients' room for dental operations.

During the early years there were frequent papers, letters and discussions on the relative merits of chloroform, ether and nitrous oxide for dental anæsthetic purposes. It was a long time before the safety and the easy administration of gas ousted the others from general use in dental practice. I remember being told by a doctor patient of mine that when he needed an extraction he usually gave himself chloroform. He sat upright in the dental chair, administered the chloroform to himself on an open mask, and told the dentist that, when his hand dropped and he was no longer able to hold up the mask he was ready for the operation to start. Happily for me he did not then require any extractions.

At a meeting of the Odontological Society held in March 1859 a paper was read by Dr. Blandy of New York advocating the use of cast base metal denture bases as better than swaged metal, ivory, or the relatively new vulcanite, and at the following meeting in April, Mr. Putnam, also of New York, spoke of the use of vulcanite.

This had been introduced in the United States by Mr. Goodyear in 1855, although Mr. Evans of Paris claims to have made some experiments for Goodyear in 1851 or 1852, and to be the first to make a practical "piece" as dentures were called.

Tomes was busy designing, not only the extracting forceps for which he was so well known, and which have, in many cases, remained unchanged to the present day, but also instruments for the insertion of fillings.

W. D. Miller of Berlin propounded in 1884 his chemico-parasitic theory of dental caries. Although it has been hotly disputed ever since, and certainly is not the whole story, it has not yet been generally discarded.

Non-cohesive gold had come into general use as a filling material early in the nineteenth century, and about 1855 Dr. Robert Arthur of Baltimore invented the method of cold welding pure gold in the cavity. Incidentally, he became a corresponding member of the Society in 1859.

In 1857 John Tomes read a paper describing a method of keeping teeth dry during filling, with a membrane of gutta-percha coated on one side with either gelatine or gum-arabic to make it adhere to the mucous membrane. Rubber dam was introduced by S. C. Barnum of New York in 1864.

The passing of the Dentists Act in 1878 and the starting of the Dentists Register, initiated a new era in dentistry. Before that time there was nothing to prevent anybody, with no surgical training whatever, holding himself out as qualified to practise, and advertising in the most blatant and outrageous manner. The new Act was designed to prevent unregistered and, ultimately, unqualified practice by prohibiting any unregistered practitioner from calling himself dentist or dental practitioner or by any name, title or description implying that he was registered or specially qualified to practise dentistry. The General Medical Council was entrusted with the duty of keeping the Register and maintaining, in the interests of the community a high standard of professional conduct. It is amusing to note that, in the discussions which took place prior to the passing of the Act there was considerable opposition to the imposition of duties of control by the General Medical Council. The *British Medical Journal* protested that "Medicine is a profession, Dentistry

is largely a business. To adjudicate upon charges likely to be brought against dentists involves some knowledge of trade matters as well as of professional matters". In spite of this, these duties were imposed upon the General Medical Council and carried out by them with the greatest care. There were at first no dental representatives on the General Medical Council and in May 1899 the British Dental Association requested the appointment of one or more. The Council replied that they had no power to do this, but the Privy Council nominated Charles Tomes as Crown nominee, in succession to Sir Richard Quain.

The Act of 1878 appears to have succeeded at first in controlling dental practice and no legal decision on it is reported until eight years later. Subsequently there were many prosecutions. Most of them were under the section which prohibits the use of titles implying registration or the possession of special qualifications. Convictions were followed by appeals, some of which were dismissed, and some allowed. Advertising by unregistered practitioners became general and blatant. The most important legal case under this Act was that of Bellerby *v.* Heyworth, which was taken to the House of Lords.

Their decision on April 15, 1910, that there was nothing in the Act which prevents any man from doing dentists' work and informing the public that he does such work, without being registered under the Act, was a statement of Law by the Supreme Court of Appeal of the United Kingdom and was unalterable except by Act of Parliament. From this time until the Act of 1921 it was quite clear that an unregistered man could not call himself a dentist or imply that he was on the Register; but that he might expatiate upon his skill in dentistry, employ any number of unqualified assistants, and advertise in the most blatant manner without hindrance.

The first Dentists Register, authorised by the 1878 Act, contained the names of 5,289 practitioners, of whom only 483 were licentiates, and it is a little surprising to find that, prior to the 1921 Act the numbers on the Register were almost the same—about 5,500. By this time, however, at least 75% were graduates or licentiates, and practically all the rest were those who had been admitted as being in practice in 1878. There were then added some 8,000 practitioners who, again, claimed to have been in practice at that time. Since then the number has increased a little, but of the 15,000 now on the Register only about 12,000 are actually practising. Very few of those registered as in practice in 1921 will remain on the active list after the next ten years, and it is probable that more than one-third of those now on the Register will have ceased to practise—a loss of about 5,000—while new registrations may number only 3,000.

It follows then, that, as our dental schools have scarcely been able to maintain the number of active practitioners, and as the Welfare State is irrevocably committed to the provision of a comprehensive dental service, there is an urgent need for steps to be taken to make good the rapidly increasing rate of loss to be anticipated in the next few years.

This is hardly the place to discuss the pros and cons of the use of ancillary workers and the provisions of schools and teachers to train them, but I cannot help comparing the era which is now beginning with the state of the profession a century ago. There was then a totally inadequate number of qualified dentists, and a large amount of the work was carried out by untrained or partly trained practitioners, and now, with the number of qualified dentists still inadequate, it is proposed to experiment with the use of partly trained operators, under the control of the General Dental Council which took over the Dental functions of the General Medical Council in 1956.

The training of the dental student in the early days of the Odontological Society was, as I have said, by apprenticeship to a dental practitioner. When the first regulations for the curriculum were laid down and training was started at the Dental Hospital of London, and the National Dental Hospital, great stress was laid upon the importance of acquiring manual dexterity. Before admission to a dental school the student had to be apprenticed for three years to a dental surgeon to learn dental mechanics. If a pupil was fortunate enough to be articled to a practitioner whose standard of work was high and who took pains to see that he was well instructed, the system was very satisfactory.

A most interesting description of the professional training of the time is to be found in the autobiographical notes of the late J. H. Badcock, published in the *British Dental Journal* in January 1954. He started in 1880, and was President of this Section in 1917.

Later the time spent at dental mechanics was reduced to two years, which could be spent either privately or in the pupils' laboratory at one of the dental schools. Before private apprenticeship was finally abolished, the regulations required either three years articles or two years at a dental school.

I did my own mechanical training with a practitioner who had a good middle-class practice at which he worked in the daytime, and in the evenings he had a dental dispensary in the Waterloo Road. Here, although the fees were low, the standard of work was good, and it had the great advantage, as far as I was concerned, that I was able, under supervision,

to take impressions, and make quite a number of dentures for patients. I was also permitted to do free extractions, without any anæsthetic, and often removed 70 or 80 teeth in one evening. We used only three pairs of forceps, as far as I remember—straights and bayonets for uppers and a pair of lower root forceps. We used to feel a sense of superiority when, as happened from time to time, patients came in who had had roots left in after attempts at extraction at Guy's. This was countered later, when I was a student at Guy's, by the appearance there of some of the failures of the Dental Dispensary.

Clinical teaching was done entirely by part-time honorary teachers, who spent the rest of their time in private practice. The first dental professor in this country was Samuel Cartwright (junior) who was appointed to the Chair of Dental Surgery at King's College, London, in 1860, but there was at that time no dental school there. The first professor to hold a Chair in a Dental School was Gilmour, who was appointed in 1920 at Liverpool. Since that time dental education has come more and more into the hands of full-time teachers.

The appointment of these teachers was a tremendous advance, as it provided opportunities for men of the highest ability in the profession to initiate projects of research, and to co-ordinate to a much greater extent the academic and clinical teaching. I would not like it to be thought that I underestimate the value of these full-time teachers. They are essential to the teaching of dental surgery as we know it to-day, but there has been, in recent years, a real danger of the clinical training becoming too academic. Of course it would be much easier administratively to organize the necessary sessions with full-time teachers, and there is still much room for improvement in the teaching, but it must never be forgotten that for a good many years to come graduates will have to spend most of their time putting in fillings, doing straightforward extractions, and replacing lost teeth with prosthetic appliances, and treating periodontal conditions. All these will be done the better for a wider knowledge of anatomy, pathology and surgery, but extension of education in this direction must never be at the expense of time spent acquiring operative skill in dentistry.

The part-time clinical teacher does, I think, still serve a useful purpose in relating the operative work of the student to the needs of private practice, an aspect difficult for him to appreciate while he is treating only hospital patients and with which the purely academic teacher is in danger of losing touch.

From the passing of the 1878 Act onwards, there was a period of scientific advance. This came mainly from the isolated efforts of individual workers, as there was little or no organized research until a much later date.

Sir John Bland-Sutton made many of his contributions to the study of dental pathology at the Odontological Society, his first paper in April 1883 being on the development of the mandible. From that time until 1905 his interests included problems of calcification of the jaws, the pathology of odontomes, of pyorrhœa alveolaris or Riggs' disease as it was then called, structure and development of ovarian teeth, treatment of caries, and after-treatment of extractions. The *Transactions of the Odontological Society* contain some 22 papers or discussions in which he took part between 1883 and 1905.

Cocaine was first introduced as a local anæsthetic about 1885, and in spite of its danger, soon came to be used extensively. Up to 1907 cocaine and the chemically related eucaine and Stovaine were the only local anæsthetics in general use. The *British Medical Journal* of March 1907 published a letter advocating the use of 20 minims of a 10% solution of cocaine, equivalent to 2 grains. On March 25, 1907, Dr. J. W. Pare gave a casual communication to the Society on Novocain, which he said had been introduced to this country in the previous June.

In February 1899 Dr. William Hunter read his paper on the Relations of Dental Diseases to General Diseases, which initiated what might be termed the era of focal sepsis. It was accepted with rather uncritical enthusiasm by the progressive members of both the medical and dental professions and for many years its validity was scarcely disputed. It was not at all unusual for the doctor who was at a loss to understand his patients' symptoms to send him to the dentist with instructions to have all his teeth out.

While dental sepsis is no longer regarded as the specific cause of the vast number of general diseases which used to be attributed to it, I think the pendulum may have swung too far in the opposite direction, and that there is some danger of the effect of oral infection being underestimated.

Dental radiographs were taken in America about 1896, and as far as I can ascertain were first shown here to the Odontological Society on January 28, 1901, when Carl Schelling read a short paper on "An obscure case of dental trouble diagnosed by X-rays". He had seen the patient 18 times, gradually dilating a sinus in the upper canine area, with bibulous paper. The patient had assured him that $\underline{3}2|$ had been extracted without fracture of the roots. The area was radiographed by Dr. Mackenzie Davidson with a piece of tinfoil in the sinus, and a root was shown to be present.

In 1895 occurred an event of major importance and interest to the dental profession, when the name of Lilian Murray appeared in the Register, the first woman to be registered. As Dr. Lindsay she is known to all of us and it would be difficult to exaggerate the debt owed to her by this Society, the British Dental Association and the profession as a whole. She was President of this Section in 1945 and of the Section of the History of Medicine in 1950.

At the end of the nineteenth century amalgam was coming into general use. It was first regarded as an inferior substitute for gold, to be used only by incompetent workers, but was not, as far as I can find out, ever held in such disrepute in this country as it was in the United States. There, at one time, the American Society of Dental Surgeons, the American Dental Association of its day, had a rule that "any member of this society who shall hereafter refuse to sign a certificate pledging himself not to use any amalgam, and moreover, protesting against its use under any circumstances in dental practice, shall be expelled from this society". Before very long, however, most members were using it surreptitiously and it seems to have become respectable there in the early 1870s. In both countries many materials were used. The alloys used were mostly proprietary, although a number of practitioners made their own. In 1895 Dr. E. V. Black published some work on amalgams, but from then until 1933, when Dr. Marie Gayler published the results of her investigations at the National Physical Laboratory, little scientific work seems to have been done on the subject. Thanks to the Dental Board, a very full study was then made, and most useful data obtained as to the factors controlling the setting of amalgams.

In 1903 Dr. Black described the fundamental principles of cavity preparation, which hold good to-day.

The special study of Orthodontics developed in the latter part of the nineteenth century, much of the interest in the subject being stimulated by the enthusiasm of Edward Angle and his followers. In this country it culminated in the foundation in 1908 of the British Society for the Study of Orthodontics, largely due to the work of the late George Northcroft, who was President of this Section in 1928.

Progress has been made in the treatment of periodontal disease, to which Sir Wilfred Fish has made important contributions.

The advances in anæsthesia which have come in the last twenty-five years, together with the general and discriminate use of antibiotics since the war, have improved enormously the results of oral surgery. When one thinks of the large numbers of impacted third molars and odontomes which we remove at the present time, one wonders what happened to them in the past. It may be that the odontomes were treated by the general surgeon and the impactions relieved by the extraction of the more easily accessible neighbouring teeth.

In the field of prosthetics, the use of acrylic resins has completely replaced vulcanite, and cast gold has taken the place of the swaged dental plate. Now the chrome cobalt alloys are to some extent replacing gold.

Advances in conservative dental surgery have been assisted by the increased use of local anæsthetics and of cold water jets for the prevention of pain. The development of painless dentistry which is at the same time safe has helped us to take advantage of the improvement which has taken place not only in plastic filling materials, but in the accurate casting of gold for inlays and bridges.

While great advances have been made during the hundred years of the life of the Odontological Society and of this Section, in the conservative, surgical and prosthetic treatment of dental disease, comparatively little has been learned about its prevention. The large-scale experiments with fluoridation of water would appear to offer some prospect of a reduction in the caries rate, but much more evidence is needed over many more years before this can be finally accepted or rejected.

A country-wide campaign of instruction in oral hygiene would bring about a great improvement, especially if, before starting it, the profession could agree upon its essentials. Nearly all of us are fully occupied in repairing damage already done, and it is only recently — since 1920—that our schools have had full-time teachers, and professors, one of whose main duties is the promotion of research, without which so little can be done in the field of prevention.

I venture to think that the next phase of dentistry, which may be only just over the brow of the hill, will be the era of preventive dentistry. The time may well come when the dentist willl examine his patient, advise, and prescribe treatment, both preventive and restorative, which will be carried out by others under his control, whose work would be analogous to that of the radiographer, the optician or the physiotherapist. The vastness of the task of controlling such widespread diseases forces us to envisage such a possibility.

It only remains for me to express my thanks to those who have helped me in the preparation of this Address, especially to Dr. Lilian Lindsay and Mr. Alan Shefford and to the Librarians of the Royal Society of Medicine, and of the British Dental Association.

JOINT MEETING No. 5

Section of Pathology with Section of Epidemiology and Preventive Medicine

Chairman—Professor JOHN W. S. BLACKLOCK, M.D.
(President of the Section of Pathology)

[*January* 15, 1957]

DISCUSSION ON ADENOVIRUS INFECTIONS

Dr. B. E. Andrews and Dr. J. C. McDonald (Central Public Health Laboratory, London):
Epidemiological Studies of Adenovirus Infection

In 1954 the distribution of serological types in a series of 143 adenovirus strains isolated in the U.S.A. was reported by Huebner and his colleagues. More recently Rowe and Huebner (1956) reviewed present knowledge of the clinical significance of these viruses. The purpose of this communication is to present the information we have obtained since 1954 on the natural distribution of adenovirus types in this country and on the illnesses with which they have been associated. Most of the observations on which our report is based were made in collaboration with others, in the course of planned surveys of acute respiratory disease in the Royal Air Force, and in the investigation of outbreaks and sporadic cases of respiratory and other febrile illness in residential schools and in the general population.

METHODS

In most of the investigations a systematic record was made of the symptoms and clinical signs in each patient. Laboratory diagnosis of adenovirus infection was usually serological and based on a fourfold or greater rise in complement-fixing antibody to the adenovirus group antigen, in paired blood samples. Virus isolation was attempted only on suitable specimens, taken from a sample of cases in each outbreak. In more than 70 patients on whom both isolation and serological tests were performed good correlation was obtained by the two methods between positive and negative results.

All but four virus strains were isolated in HeLa cell cultures, the presence of virus being detected by the characteristic type of degeneration caused, and by the production of the group complement-fixing antigen. The type of virus was identified by neutralization tests in HeLa cultures using type-specific rabbit sera. All strains were tested against sera to adenovirus types 1 to 8; when they were not neutralized by any of these they were tested against a serum to type 14, kindly supplied by Professor van der Veen. The laboratory techniques have been more fully described elsewhere (Kendall *et al.*, 1957).

DISTRIBUTION OF ADENOVIRUS TYPES

Results of typing of 85 selected adenovirus strains isolated in this country since 1954 are presented in Table I, classified into broad clinical and age groups. Some 200 strains were isolated in this period but it was not possible to undertake the typing of them all. In choosing those to be tested, strains were taken from as many different outbreaks and clinical conditions as possible and no attempt was made to examine all the strains available from any particular source. Of the 85 strains shown in Table I, 63 were from 14 outbreaks and 22 from sporadic cases. Most of the strains were isolated from throat swabs taken during the acute stage of illness, but some were from eye swabs and some from fæces; 4 strains were from tonsils and adenoids removed at operation.

The virus strains from the tonsils and adenoids were of types 1, 2 and 5. The only other type 1 strain was from the lungs of a baby aged 3 months that died from pneumonia. Type 2 virus was isolated from a fatal case of pneumonia in a child aged 3 months, from a child aged 6 weeks with acute bronchiolitis, and from 3 patients thought to be suffering from non-paralytic poliomyelitis—aged 2, 6 and 26 years respectively. Twelve strains belonging to type 3, representing 3 large outbreaks in schools and 2 sporadic cases, came from patients with the clinical features of pharyngo-conjunctival fever. Few strains of types 4 and 5, and none of type 6 were encountered. Type 7 was, in our experience, the most prevalent type; it was isolated under every clinical heading shown in Table I, except tonsils and adenoids. We have not found any strains of type 8 so far. Many of the strains tested were from patients with conjunctival inflammation, but only one patient was considered clinically to be suffering from epidemic keratoconjunctivitis. This disease has been reported by Jawetz *et al.* (1955) to be due to type 8 virus in North America. Type 14 was isolated from an airman in an outbreak of febrile catarrh and from 6 boys in a school outbreak of pharyngo-conjunctival fever. One strain from a case of febrile catarrh in a military outbreak proved untypable with the sera available and Dr. W. P. Rowe has reported that it is not of types 1 to 14 inclusive.

TABLE I.—ADENOVIRUS TYPES IN RELATION TO AGE AND CLINICAL GROUP
(85 virus strains from 14 outbreaks and 22 sporadic cases)

Clinical and age group	Virus type 1	2	3	4	5	6	7	8	14	Undesignated
Tonsils and adenoids removed at operation ..	1	2			1					
Acute respiratory disease without conjunctivitis										
0–2 years	1	2					1			
3–10 years							3			
Adults—civilian ..				1			1			
military ..				1			26		1	1*
Acute respiratory disease with conjunctivitis ..			12	1			16		6	
Febrile illness with meningism		3			1		4			
Total	2	7	12	3	2	0	51	0	7	1

*This strain was not neutralized by antisera to types 1–14 (Rowe, 1957).

CLINICAL GROUPS

Many outbreaks and sporadic cases of febrile illness of unknown ætiology—mostly with respiratory or nervous symptoms—were studied between 1954 and 1956. In almost all those in which evidence of adenovirus infection was found, respiratory tract symptoms and signs were prominent. A possible exception to this was a small outbreak in a country town in south-west England, and some scattered sporadic cases, reported as "non-paralytic poliomyelitis", during the summer of 1956. These illnesses were characterized by fever, meningism that was definite and persisted for several days, and the absence of respiratory symptoms, except for a few with sore throat.

Most of the respiratory illnesses associated with adenovirus infection occurred in outbreaks and fell into two distinct clinical groups, one apparently similar to the acute respiratory diseases in military recruits described by Hilleman *et al.* (1955), and the other to the disease named pharyngo-conjunctival fever by Bell *et al.* (1955). Our experience of pharyngo-conjunctival fever is based on outbreaks in residential schools in summer (Kendall *et al.*, 1957) and of the other syndrome on surveys in the R.A.F. in winter, when it was found to be highly prevalent in recruit camps but infrequent in other types of unit (Andrews *et al.*, 1956, and unpublished data). In both types of illness the patients had four or five days' fever and fairly severe sore throat, but whereas pharyngo-conjunctival fever was characterized by enlarged cervical lymph glands, conjunctivitis and the absence of respiratory tract involvement below the pharynx, in the recruit-disease the cervical glands and conjunctivæ were usually normal, but laryngitis, tracheitis or bronchitis were frequent, and evidence of pneumonia was present in about 10% of those admitted to hospital. The main clinical features of these two manifestations of adenovirus infection are set out in Table II, together

TABLE II.—CLINICAL FEATURES OF ACUTE RESPIRATORY ILLNESS ASSOCIATED WITH ADENOVIRUS, INFLUENZA VIRUS AND STREPTOCOCCAL INFECTION

Clinical features	Pharyngo-conjunctival fever (adenovirus)	Acute respiratory disease of military adults (adenovirus)	Streptococcal pharyngitis	Influenza (A and B)
Symptoms				
Sore throat	⊞	⊞	⊞	+
Cough		⊞		⊞
Nasal	+			+
Aches and pains				⊞
Sweating		+	⊞	⊞
Signs				
Conjunctivitis	⊞			
Enlarged cervical glands	⊞		⊞	
In pharynx	+	+	⊞	+
Below pharynx		⊞		⊞

+ = present in majority. ⊞ = prominent.

with those of influenza and streptococcal pharyngitis for comparison. It is our impression that in epidemics at least, it may often be possible to distinguish these 4 syndromes from each other clinically, though not necessarily from infections due to other agents.

SUMMARY AND CONCLUSIONS

From some 200 adenovirus strains isolated in England since 1954, 85 taken from 14 outbreaks and 22 sporadic cases were typed. Representatives of types 1, 2, 3, 4, 5, 7, 14 and an undesignated type were identified. 9 of the 11 strains of types 1, 2 and 5 were from tonsils and adenoids removed at operation or from acute respiratory disease in infants under 3 years of age. Of the remaining 74 strains, 51 belonged to type 7 and were isolated from patients of all age-groups in a variety of clinical categories.

With the exception of a small outbreak and some sporadic cases in which the main symptoms were fever and meningism, laboratory evidence of adenovirus infection has only been found in patients with acute respiratory disease. These respiratory illnesses fell into two clinical groups, both with fever and pharyngitis but one accompanied by conjunctivitis and cervical lymphadenopathy, and the other by tracheitis, bronchitis and sometimes pneumonia. The latter illness was almost confined to military recruits in the winter months, and the pharyngo-conjunctival illness to children in residential school outbreaks.

No constant relationship between adenovirus type and clinical syndrome has been apparent.

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Dr. H. G. Pereira and **Barbara Kelly** (Common Cold Research Unit, Harvard Hospital, Salisbury, Wilts): *Studies on Natural and Experimental Infections by Adenoviruses*

Adenoviruses have been associated with a variety of human infections occurring sporadically or epidemically, especially in military populations. Of the 14 serological types so far identified (Rowe *et al.*, 1956) some are more frequently associated with outbreaks of disease and others are found as "latent" viruses in adenoids or tonsils and occasionally causing sporadic infections.

The ætiological role of adenoviruses types 4 and 7 in acute respiratory disease (A.R.D.) or febrile catarrh (Hilleman *et al.*, 1955; Berge *et al.*, 1955) and of adenovirus type 3 in pharyngo-conjunctival fever (Bell *et al.*, 1955) has been clearly demonstrated. Some cases of primary atypical pneumonia have also been related to type 4 infections (Hilleman *et al.*, 1955; Berge *et al.*, 1955). There is some evidence that adenovirus type 8 is the cause of epidemic keratoconjunctivitis (Jawetz *et al.*, 1955). A number of less clearly defined respiratory infections have been associated with other types of adenoviruses and it has been suggested that these viruses may be related to some cases of mesenteric lymphadenitis (*see* reviews by Rowe and Huebner, 1956, and by Dingle and Feller, 1956).

Work on volunteers (Bell *et al.*, 1956; Southam *et al.*, 1956; Roden *et al.*, 1956) has confirmed the pathogenic action of several types of these viruses and demonstrated the relation between susceptibility to infection and pre-existing antibodies.

Our interest in this group of agents was initially stimulated by their possible ætiological relationship with the common cold. Clinical, epidemiological and experimental studies had previously established certain criteria for distinguishing the common cold from several different "entities" among the group of unclassified upper respiratory infections (Stuart-Harris *et al.*, 1938; Commission on Acute Respiratory Diseases, 1947). By means of the methods now available for the study of serological responses to adenovirus infections, Ginsberg *et al.* (1955) were able to confirm the identity of "acute respiratory disease" as a distinct entity and to demonstrate the ætiological relation of adenovirus type 4 (R.I.67) with this disease. No relation of this adenovirus to the common cold could be demonstrated by these authors. This last finding is substantiated by our own failure to recover

adenoviruses from nasal washings obtained from natural or experimentally induced cases of common cold. A total of 42 such washings tested in HeLa cells gave entirely negative results after prolonged observation of the test cultures and, in most cases, after several blind passages. Several instances of isolation of adenoviruses from cases diagnosed as common cold are recorded in the literature but in view of the diagnostic difficulties in this group of diseases these observations are to be expected and their relative rarity is in favour of an independent ætiology of the common cold.

Our studies on specially recruited volunteers (Roden *et al.*, 1956) provided both clinical and laboratory evidence of an ætiological relationship between adenovirus type 1 and a respiratory illness best described as acute pharyngitis. Clinical and subclinical infections were observed and susceptibility of volunteers to this virus was closely correlated with the absence of pre-existing homotypic serum neutralizing antibodies. The study of the serological responses revealed, as for other adenovirus infections, the group specificity of the complement-fixing antibodies. The serum-neutralization test was more type-specific but frequent heterotypic responses were observed indicating that in individual cases, the serological tests alone were insufficient to establish the identity of the infective virus type.

Our experience with infections by other types of adenoviruses include a few sporadic cases of respiratory illnesses caused by types 1 and 5 and a small outbreak of pharyngo-conjunctival fever caused by a strain related to type 7.

A strain of adenovirus type 1 was isolated in our laboratory from tracheal and lung swabs collected *post mortem* from a case of pneumonitis in a 4½-months-old child. A similar observation was made in the U.S.A. by Henle (quoted by Rowe and Huebner, 1956) and an adenovirus type 3 has been isolated in Holland by Dr. van der Veen (personal communication) from the lung of a fatal case of pneumonitis in an 8-months-old child. The ætiologic association of adenoviruses with these cases cannot be definitely established but these observations suggest the need for further study of the problem.

In December 1955–January 1956 a small outbreak of pharyngo-conjunctival fever associated with an adenovirus strain related to type 7 was observed in Salisbury. Most of the cases observed by us occurred among young children. 3 households were observed and at least 1 child from each house had prolonged and repeated contact with those of the other 2. Of a total of 15 members of the 3 households (7 adults and 8 children), there were 10 cases of infection, 3 in adults and the remainder in children between 1 and 7 years old. Most patients had fever, pharyngitis, rhinitis and cervical adenitis. 3 patients, 2 adults and 1 child, had unilateral conjunctivitis and pre-auricular adenitis. Virus isolations were attempted from 6 cases with positive results in all but one. The positive isolations were from nose and throat swabs in 2 cases, from throat swab in 1 case and from conjunctival swabs in 2 cases. Of the 3 cases of conjunctivitis, virus was isolated from conjunctival swabs in 2 and not attempted in the third. The sequence of events was suggestive of an incubation period of four to six days. All the viruses isolated from these cases were shown to belong to the same type provisionally designated as type 7-H. Comparison of a representative strain from this outbreak with adenovirus prototypes 1 to 11 by means of neutralization tests in cultures of HeLa cells using rabbit anti-sera revealed no cross reactions with any but adenovirus type 7. The cross reactions with this type are shown in Table I.

TABLE I.—CROSS REACTIONS BETWEEN ADENOVIRUS TYPE 7 AND TYPE 7-H BY SERUM-NEUTRALIZATION TEST

	Strain	
Anti-serum	Type 7	Type 7-H
Type 7	6,400	800
Type 7-H	400	1,600

Other strains of the same type were isolated by Dr. M. S. Pereira at the Salisbury Public Health Laboratory; 2 in May 1956—associated with cases of upper respiratory infections in Salisbury; and one in June 1956 from a case of conjunctivitis in a patient just arrived from Cornwall. Similar outbreaks caused by the same type of adenovirus were observed by Dr. D. A. J. Tyrrell in Sheffield during the same winter (Tyrrell *et al.*, 1956).

Two strains of adenovirus type 7-H were isolated from cultures of adenoids received during the first few months of 1956 from Mr. Brian Reeves, the E.N.T. surgeon in Salisbury. It may be worthy of notice that one of these was from the adenoids of a child who had had, four months previously, a type 7-H infection, confirmed by virus isolation, during the outbreak just described.

These findings confirm the association of adenovirus type 7-H with pharyngo-conjunctival fever, a disease previously related mainly to adenovirus type 3.

The limited studies so far reported do not allow us to make a judgment on the exact importance of adenoviruses as a source of disease in this country. Further knowledge in this field will be most valuable in view of the good prospects of artificial immunization against this group of agents.

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Dr. R. G. Sommerville (The Virus Laboratory of the University Departments of Bacteriology and of Infectious Diseases, Ruchill Hospital, Glasgow): *Adenoviruses as a Cause of Epidemic Keratoconjunctivitis on Clydeside*

As an example of the amount of illness and morbidity which can be caused by one adenovirus I would like to describe an epidemic of keratoconjunctivitis which occurred in the west of Scotland between November 1955 and October 1956. A preliminary analysis of the details up to the end of August 1956 was made by Dr. J. Winning of the Eye Infirmary, Glasgow, and I am grateful to Dr. Winning and to other clinical colleagues for permission to quote from it. A full report of the outbreak will be published shortly.

The epidemic began in workers in one shipyard and quickly spread to involve most sections of heavy industry in the Clyde Valley. It is difficult to be certain of the total number of cases in an illness of this nature, due mainly to the fact that a choice of several ophthalmological clinics was available and also because many patients who were mildly affected, sought treatment from works ambulance rooms or general practitioners only. The figures on which this report is based were drawn from two clinics and the number involved in the nine months to the end of August 1956 was around 1,700. The total number of cases in the area was probably very much greater.

Analysis revealed that 83% of patients were male and a large proportion were workers with metal. One of the most puzzling features of the outbreak was the almost complete lack of spread from the infected male to his family, despite the highly infectious nature of the illness. Approximately 50% of cases involved the right eye, 30% the left and 20% both eyes. The incubation period of the disease was calculated to be between seven and ten days.

Few patients developed fever during the illness and a typical case might be represented as follows: the onset was abrupt with a gritty feeling in the eye and lacrimation. These were rapidly followed by conjunctivitis, chemosis, follicle formation and in some cases membrane formation in the lower conjunctival fornix. Pre-auricular adenitis was present in the majority of cases and often was the presenting sign associated with earache. Four or five days later subepithelial corneal opacities developed and these are a typical feature of the disease. Within a few days these ulcerated and corneal sensation was lost. Re-epithelialization occurred within two to four weeks and thereafter resolution gradually followed. With re-epithelialization the pain and irritation frequently returned and lasted perhaps for some months.

Many different treatments were tried and most were unsuccessful, but chloramphenicol ointment, probably merely by suppressing bacterial contaminants, was the treatment which appeared to confer most benefit. Relapse occurred in about 4% of cases, and usually the same eye was affected with a rather more severe attack than the first. Diminished visual acuity was troublesome, especially where both eyes were affected and about 10% of cases were ill for more than three months altogether.

As a result of this preliminary analysis 2 cases have been discovered where a rheumatoid type of arthritis developed during the early weeks of keratoconjunctivitis. One of these patients is a medical practitioner, and both illnesses have since cleared up.

Laboratory Studies

Virus isolation was attempted from conjunctival swabs in tissue culture. Each swab was extracted in a few millilitres of buffered saline with added antibiotics and the fluid was examined in tissue culture of HeLa cells. Forty-nine such swabs yielded negative results. One swab produced an adenovirus. No virus was isolated when the swab extract material was

inoculated into eggs and suckling mice intracerebrally. Extracts of fæcal specimens from 8 patients were examined in tissue culture of HeLa cells and from one an adenovirus was isolated. A conjunctival swab from this case was negative in tissue culture.

Both adenoviruses belonged to type 3 and unfortunately it was not subsequently possible to contact these patients to obtain serum for neutralization tests. Complement-fixing (C.F.) antibody for the adenovirus group antigen develops rapidly and increases in amount as the disease develops. The rising titre of C.F. antibody in a representative group of cases is shown in Table I. Acute specimens were all collected in the first ten days of illness and the convalescent sera were collected at the intervals shown.

TABLE I.—COMPLEMENT-FIXATION TESTS WITH RI-67 ANTIGEN

Case	Acute*	Convalescent	Interval (weeks)
3	<8	16	4
6	<8	32	4
7	16	16	1
8	<8	16	2
11	<8	16	2
12	16	64	3
16	8	16	1

* Acute sera collected during first ten days of illness.

TABLE II.—NEUTRALIZATION TESTS WITH ADENOVIRUS TYPES 3 AND 8

Case	Type 3 Acute*/Conv.	Type 8 Acute*/Conv.	Interval (weeks)
3	8/8	<8/16	4
6	4/8	<4/256	4
7	4/4	8/16	1
8	16/16	<8/64	2
11	<4/<4	<8/32	2

* Acute sera collected during first ten days of illness.

Serum virus neutralization tests were performed in tissue cultures of HeLa cells against adenovirus types 3 and 8 only. All sera tested to date have developed neutralizing antibody to type 8 virus after the first ten to fourteen days of illness. A representative selection of results is shown in Table II. A small rise in titre of neutralizing antibody to the type 3 virus has also been observed in some cases, but despite the isolation of two type 3 viruses, no cases have been found with significantly rising titre of neutralizing antibody to this virus.

From the evidence which I have reviewed this epidemic of keratoconjunctivitis appears to have been caused by adenovirus type 8 and this finding is in agreement with recent experience of the disease by Jawetz *et al.* in U.S.A. (1955) *Amer. J. Ophthal.*, **40**, 200.

Dr. P. K. Hopper: In view of the evidence that adenovirus is formed as aggregations within the cell nucleus, I would be interested to hear if any intra-nuclear inclusion bodies were found in smears taken from the cases with conjunctivitis.

As this virus seems to persist as a latent infection in adenoids and tonsils, and thereby act as a continual antigenic stimulus, it would be interesting to know if children who have had their tonsils and adenoids removed are more susceptible to infection with different types of virus of this group.

(Reply: No observations on this point were made in the studies described.)

Whilst considering the possible role of trauma in conjunctival infections with this virus, I think some observations made in America by Dr. R. J. Huebner (personal communication) two years ago are very relevant. Several types of adenovirus were tested in volunteers by the conjunctival route, and it was found that in many cases infection could not be initiated unless some degree of trauma was caused with the inoculating swab.

Dr. C. H. Smith, in reply to Dr. Hopper, said that in his experience inclusions were not found in scrapings taken from human conjunctivæ in these infections, although the nuclei of the conjunctival cells often showed a marked degenerative change.

Mr. Barrie R. Jones (Moorfields Eye Hospital): *Sporadic Ocular Disease Associated with Adenovirus Infection in London*

During 1950 over 80 cases of a rather distinctive conjunctivitis, resembling that which Dr. McDonald has just described, presented in the Ophthalmic Department of the Dunedin Hospital in New Zealand. This was found to be associated with a glandular fever-like illness which was epidemic at the time (Jones *et al.*, 1952, *Proc. Univ. Otago med. Sch.*, **30**, 1). The conjunctivitis was usually preceded, accompanied or followed by upper respiratory infection, fever, malaise and pre-auricular or cervical adenitis. In some cases the adenitis was widespread, the abdominal nodes being not infrequently involved. These cases were characterized by the development of a total mononucleosis of more than 50% with 5% or more of abnormal lymphoid cells, and negative Paul Bunnell tests. Similar sporadic cases were seen at Moorfields Eye Hospital in 1952, 1953 and 1954. Although a few abnormal lymphoid cells were usually present some cases did not show an increase in total mononuclears.

In 1955 when Dr. R. W. Riddle invited me to see some of his boys at Lancing College who were suffering from adenovirus infection, I was impressed by the very great clinical similarity and fully expected that this would be the answer to a great deal of our previously unidentified ocular infections.

During 1956, working with Dr. B. E. Andrews at the Virus Reference Laboratory and Drs. G. A. Henderson and P. B. Schofield at the Institute of Ophthalmology I have investigated a proportion of the acute conjunctivitis and keratoconjunctivitis presenting at Moorfields and the London Hospital. Evidence of adenovirus infection was obtained in 7 of the first 60 cases (Table I). In 4 cases there was at least a fourfold rise in titre to the

TABLE I.—LABORATORY FINDINGS IN 8 CASES OF OCULAR ADENOVIRUS INFECTIONS

Case No.	Day of ocular disease	Day of systemic disease	Adenovirus C.F.T.	Systemic illness	Virus isolation and day of disease in that site	Type of adenovirus
25	4	3	1 : 2	Severe	L. eye (4)	4
	17	16	1 : 32	8 months	Throat (3)	
32	5	5	1 : 2	Moderate		
	36	36	1 : 16	2 weeks	Nil	?
49	3	3	1 : 4	Minimal	L. eye (3)	7
	18	18	1 : 16	5 days	Throat (3)	
53	8	3	1 : 2	Moderate	Not yet completed	?
	22	17	1 : 8	1 month		
	36	31	1 : 16			
57	5	8	1 : 2	Mild	R. eye, L. eye (5)	7
	20	23	1 : 4	2 weeks	Throat (8)	
	48	51	1 : 4		L. cornea (9)	
61	4	12	1 : 8	Fairly	L. eye (4)	3
	18	26	1 : 32	severe	Throat (12)	
				2 months		
80	7	10	1 : 4	Moderate	Nil	?
	21	24	1 : 16	1 month		
81	3		1 : 8	Nil	R. eye (3)	7
	17		1 : 8			

complement-fixation test (C.F.T.) and adenovirus was isolated from the affected eye of 3 of these. In 2 further cases adenovirus was isolated from the inflamed eye of patients who had some complement-fixing titre but did not show a fourfold rise. These were cases with minimal systemic disease. Virus was isolated from the throats of 4 of the 5 cases in which there were signs of pharyngitis accompanying the conjunctivitis. Virus isolation was not successful in 2 further cases which showed a fourfold rise in C.F.T. titre. Types 3, 7 and the "Dutch type" of virus at Lancing College produced a pharyngo-conjunctival fever resembling that reported from America in type 3 virus infections, and type 8 virus was responsible for the Glasgow epidemic keratoconjunctivitis. Hence it is of interest to know whether there is any correlation between the virus type and the pattern of illness in the sporadic London ocular cases (Table II).

With each type of virus the conjunctivitis was similar; there was some ptosis and slight swelling of the lid, but no purulent discharge. The inflammation was most marked in the lower palpebral conjunctiva with the bulbar and upper lid conjunctiva rather less involved. In all except Cases 53 and 32 the inflammation was follicular and the pre-auricular node was always palpable and usually tender. The differences lay chiefly in the nature of corneal and systemic involvement. The type 3 infection did not affect the cornea and was associated with a moderately severe upper respiratory infection with headache and cervical adenitis, leading on to abdominal pains and tenderness with some diarrhœa. Fever, malaise and abdominal symptoms persisted intermittently for two months. In the type 4 virus infection the cornea was not affected and it was accompanied by moderately severe upper respiratory disease with pre-auricular and cervical adenitis, headache and myalgia which went on to abdominal, inguinal and cervical adenitis with episodes of slight diarrhœa. His white cell count rose steadily to 24,000 in the fourth month and has now subsided to 12,000. Early on there were abnormal lymphoid cells although the response was chiefly polymorphonuclear. Although the glandular and abdominal symptoms have been recurrent and the patient has shown a gradual improvement, he has not been apyrexial for more than a day at a time since this glandular fever-like illness began eight months ago.

One case in which no virus was isolated was accompanied by coryza, sore throat, cervical adenitis and palpable spleen. The lymphadenitis, fever and malaise took one month to resolve. A further case in which no virus was isolated was accompanied by a fine punctate epithelial keratitis in which the lesions were not visible until stained by fluorescein and they cleared completely. The ocular infection was followed by sore throat, headache, soreness of neck muscles, anorexia and vomiting. Cough and central chest pain persisted for a month and there was a return of abdominal pain with tenderness and diarrhœa. The cervical, inguinal and abdominal nodes were enlarged in a patchy way and the spleen became palpable. There are close resemblances between these 4 cases and those of the Dunedin epidemic of 1950. The type 7 virus infections showed less systemic illness and more corneal disease. One

TABLE II.—CLINICAL FEATURES OF 8 OCULAR ADENOVIRUS INFECTIONS

Virus type	Case No.	Sex Age	Conjunctivitis	Keratitis	Systemic illness
3	61	F 26	L. follicular	Nil	Preceded by coryza, accompanied by sore throat and cervical adenitis, followed by headache, muscle pains, abdominal pain, tenderness and diarrhœa, fever and malaise for 2/12
4	25	M 26	L. follicular	Nil	Accompanied by coryza, sore throat, headache and cervical adenitis, followed by muscle pain, abd. pain and tenderness and diarrhœa, inguinal, axillary and cervical adenitis, fever and malaise for 3/12
?	53	F 21	R. and L. finely granular	Fine epithelial punctate staining with fluorescein	Followed by headache, neck soreness, sore throat, cough and chest pain, anorexia, vomiting, tender colon, palpable spleen, malaise, mild cervical and inguinal adenitis for 1/12
?	80	F 10	L. follicular and bulbar	Nil	Accompanied by coryza, sore throat, cervical adenitis and palpable spleen. Lymphadenitis, fever and malaise for 1/12
7	49	F 32	L. follicular	Nil	Mild fever and malaise for five days
7	57	M 21	L. follicular	Fine epithelial S.P.K. on ninth day progressing to subepithelial opacities of E.K.C. type on fourteenth day	Preceded by coryza, and fever for two weeks
7	81	M 33	R. follicular	Fine epithelial S.P.K.	Nil
?	32	F 6	R. finely granular	Nil	Accompanied by upper respiratory infection and fever for two weeks
			R. acute dacryoadenitis		

patient showed no systemic signs, another had mild malaise with fever for a few days, and the third had an upper respiratory infection with fever for two weeks.

In one case the cornea was not involved. In another there was a moderately severe fine epithelial punctate keratitis. The lesions could be seen only with the corneal microscope; they stained faintly with fluorescein, were associated with minimal subepithelial infiltration and cleared completely.

The third case ran a course which was clinically extremely similar to the Glasgow epidemic keratoconjunctivitis. As the conjunctivitis was subsiding on the ninth day there was fine epithelial punctate keratitis. Some of these lesions developed subepithelial infiltrations which, by the fourteenth day, had hardened to the typical disc-like opacities. Two months later these two subepithelial opacities could be seen easily with the naked eye and were exactly like the epidemic cases which Dr. J. Winning had shown me in Glasgow. Had the patient not been closely questioned and examined he would not have complained of any systemic upset.

It will probably never be decided whether the Dunedin epidemic was an adenovirus infection, but since dacryoadenitis was a feature of some cases I have also been investigating patients with inflamed lacrimal glands. Of the first 7 cases 1 showed a rise in adenovirus C.F. titre from 1 : 2 to 1 : 16 during the illness (*see* Table I, Case 32). When swabs were taken the inflammation was starting to wane, and no virus was isolated.

It is thus apparent that adenovirus infections should be considered in the differential diagnosis of glandular fever-like illnesses and that the adenoviruses are an important cause of external ocular inflammation among those cases which are severe enough to reach ophthalmic clinics, but many more cases will have to be seen before one could predict which type was responsible for a given infection.

Furthermore I should like to emphasize that several very similar cases of ocular and systemic illness have been seen in which there has been no evidence whatever of adenovirus infection. Hence whilst an adenovirus infection may be suspected clinically it can be diagnosed only in the laboratory.

Major R. J. C. Hart said that low titre complement-fixing antibodies to the adenovirus group were present in the sera of many soldiers and he suggested that these antibodies might therefore be comparatively long-lasting.

Section of Endocrinology

President—T. RUSSELL FRASER, M.D., F.R.C.P., D.P.M.

[*November* 28, 1956]

DISCUSSION ON CUSHING'S SYNDROME

Dr. R. I. S. Bayliss: *Diagnosis of Cushing's Syndrome*

There may be difficulties in establishing a diagnosis of Cushing's syndrome and, having established the diagnosis, in deciding whether the cause is hyperplasia, an adenoma or a carcinoma of the adrenal gland or even one of the other conditions (carcinoma of the pancreas, thymus or bronchus) which may rarely be present. In his original description Cushing (1932) included only patients who were severe examples of the syndrome. All had adiposity of the trunk with sparing of the limbs, kyphosis with rounding of the shoulders, amenorrhœa or impotence, hypertrichosis, purple striæ, a plethoric complexion, hypertension and backache, abdominal pain, fatigue or weakness. But even in long-standing cases several of these features may be absent, and in the earlier stages the clinical picture is less obvious. Although Cushing considered the condition a pluriglandular disorder, all its clinical and biochemical and most of its pathological features can be induced with hydrocortisone, and we now believe that increased secretion of adrenocortical hormones is the cause. Thus it is logical to seek confirmation of the diagnosis by obtaining biochemical evidence of increased adrenocortical activity. The adrenal cortex secretes many different hormones, and those that produce Cushing's syndrome belong to the glucocorticoid group having a hydroxyl group at the C-17 and usually a hydroxyl or ketone group at the C-11 positions. Large amounts of hydrocortisone were first isolated from a patient with Cushing's syndrome by Mason and Sprague (1948), and subsequently excess of cortisone and compound S (17-hydroxy-11-desoxycorticosterone) has been found in the urine of other patients (Dohan *et al.*, 1955). Theoretically excessive formation of corticosterone might cause Cushing's syndrome but no instance of this has yet been reported although increased amounts may arise in parallel with overproduction of hydrocortisone (Sweat, 1955). In some cases increased secretion of glucocorticoids is accompanied by enhanced production of androgenic steroids, and the clinical features of hyperadrenalism may range from classical Cushing's syndrome at one end of the scale to virilization at the other with intermediate forms in between. If retained at all, the term Cushing's syndrome should be reserved for patients with the clinical features of excess glucocorticoid secretion, but wherever possible, especially in mixed cases, the disorder should be classified in terms of the particular steroids secreted in excess.

Clinical cases.—In 36 patients suspected clinically of having Cushing's syndrome, the diagnosis has been confirmed by clinical and hormonal assessment in 19, most of whom have undergone total or partial adrenalectomy. In 14, excess glucocorticoid secretion was not found and the diagnosis was discarded. In 3 patients the diagnosis has remained uncertain.

Fig. 1 shows the principal features in the 19 patients with Cushing's syndrome, of whom 12 were women and 7 men. Of diagnostic importance was the alteration in skin texture which is difficult to quantitate and which was first stressed by Parkes Weber (1926). The skin loses its elasticity and can be picked up in the fingers with an absence of the normal underlying fat. The lack of elasticity and resistance is particularly noticeable when doing a venepuncture. This atrophy, which may be associated with increased bruisability and ecchymoses, is probably due to loss of body protein. The development of purple striæ seems to depend on the combination of this with truncal obesity.

Radiological evidence of osteoporosis, difficult to detect in its early stages, was found in 11 of the 19 patients. 4 patients with particularly long-standing or florid disease had fractures of the ribs, vertebræ or femur. In 1, fractures were the presenting symptom, and this patient had the highest level of 17-hydroxycorticosteroids yet encountered—88 μg. per 100 ml. All but one of the women had facial hirsutism, and of the 10 who were pre-menopausal and had not had a hysterectomy, 6 had amenorrhœa. Hypertension was a common finding,

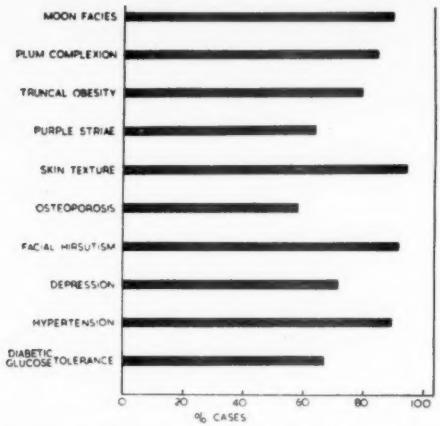


FIG. 1.—Frequency of chief manifestations in Cushing's syndrome (19 cases).

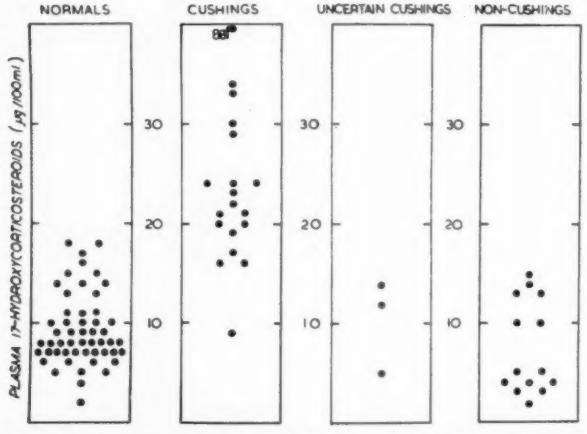


FIG. 2.—Plasma 17-hydroxycorticosteroid values in normal subjects, patients with Cushing's syndrome, patients with probable Cushing's syndrome and patients referred as having, but not found to have, Cushing's syndrome.

and headaches with failing vision and the retinal changes of malignant hypertension were the presenting symptoms in 4 patients. Mental changes, particularly depression, occurred in three-quarters of the patients. Glycosuria was not common but a diabetic glucose tolerance curve was obtained in 12 out of 18 patients. In all, the serum electrolyte levels were normal nor was a low eosinophil count in the peripheral blood of diagnostic value.

The plasma 17-hydrocorticosteroid levels are shown in Fig. 2. In most instances the value was above the upper limit of normal, 18 μg. per 100 ml., but often not strikingly so. In 5 patients the level was within the normal range, but the infusion of ACTH caused a greater adrenal response than occurs in normal subjects (Fig. 3). The urinary excretion of 17-ketosteroids (Fig. 4) was raised in some patients but abnormal values were not found as often as increased plasma 17-hydroxycorticosteroid levels. Although high 17-ketosteroid values may confirm the existence of adrenal disease, normal values in no way exclude Cushing's syndrome.

One patient had a pituitary chromophobe adenoma compressing the optic chiasma and ballooning the sella turcica; the state of his adrenal glands is not known. 3 patients had an adrenal adenoma. 11 had bilateral hyperplasia and in 4 the adrenal glands appeared normal at operation and on histological examination. This anatomical normality of the adrenals

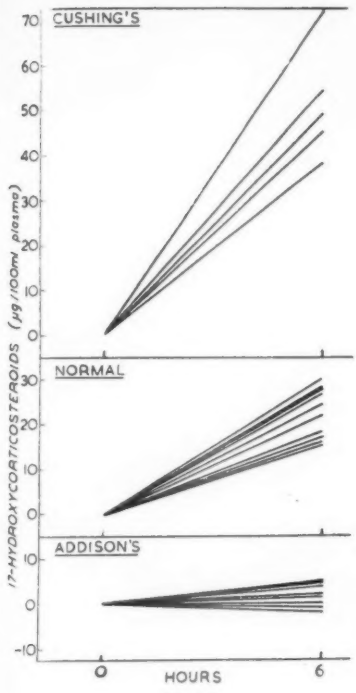


FIG. 3.

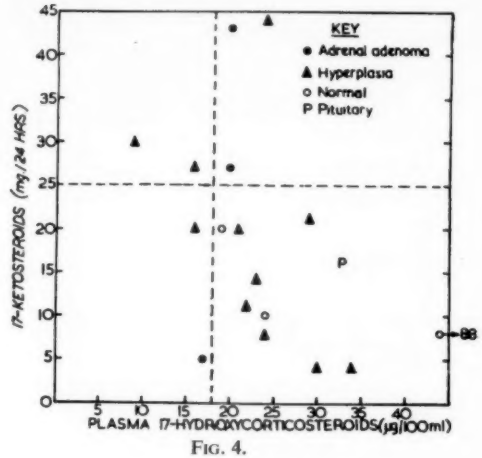


FIG. 4.

FIG. 3.—The adrenocortical response, as measured by the increment in plasma 17-hydroxycorticosteroids, to a six-hour infusion of ACTH (2 units per hour) in patients with Addison's disease, in normal subjects, and in patients with Cushing's syndrome who had a normal control value of plasma steroids.

FIG. 4.—Comparison of urinary 17-ketosteroid excretion per twenty-four hours and plasma 17-hydroxycorticosteroids in patients with Cushing's syndrome. The symbols (*see* key) indicate the adrenal pathology. Dotted lines show upper limits of normal steroid values.

in some cases of Cushing's syndrome has been observed by Cushing (1932) and more recently by Sprague (1953).

Three women, aged 41, 42 and 53, presented difficult diagnostic problems. They had amenorrhœa, moon facies, truncal obesity and facial hirsutism, but no striæ, skin atrophy or osteoporosis. 2 had diabetic glucose tolerance curves, and 2 were severely hypertensive. The plasma 17-hydroxycorticosteroid and urinary 17-ketosteroid values were normal. In 2 the response to a six-hour infusion of ACTH was greater than normal. In the third this was not measured and the patient had a subtotal adrenalectomy. Hypertension of 230/130 has persisted, but headaches and retinal changes have subsided; her "Cushingoid" appearance has regressed, and she is no longer diabetic on maintenance therapy with 12·5 mg. cortisone twice daily. The other 2 patients are still under observation.

In 14 patients clinical and biochemical evidence failed to establish a diagnosis of Cushing's syndrome. In 5, obesity was confined to the trunk but was more generalized in the others who had fat pads on the backs of their fingers. Without hormone assays it was particularly difficult to assess post-menopausal hypertensive women with round, plethoric faces who had gained weight and had an abnormal glucose tolerance curve.

Hormone assays.—Chemical methods for calculating adrenocortical hormones are difficult because of the large number formed and because in both urine and plasma they are present in conjugated and unconjugated forms (Bongiovanni and Eberlein, 1955). The method of Norymberski *et al.* (1953) is recommended for measuring the urinary excretion of glucocorticoids and their metabolites. The technique of Nelson and Samuels (1952) for estimating unconjugated plasma 17-hydroxycorticosteroids is useful but unsuitable for routine use. In most cases of Cushing's syndrome increased amounts of glucocorticoids can be demonstrated in urine and plasma by these methods. Sometimes the plasma level may be more informative than the urinary excretion, and Jailer and his colleagues found in 2 patients that repeated urinary assays were normal whereas on four out of five occasions the plasma levels were abnormally high (Wallace *et al.*, 1955).

How are the normal urinary or plasma corticosteroid levels found in some patients with undoubted Cushing's syndrome to be explained? Sometimes perhaps a steroid is secreted

which is not estimated by the method used (for example corticosterone is not measured by the Nelson and Samuels' technique). In other patients marked day-to-day fluctuations in adrenocortical activity may necessitate repeated estimations being made (Birke *et al.*, 1956). Another difficulty may be that adrenocortical activity is only slightly greater than normal. Normally adrenal activity varies throughout the day, secretion being lowest during the night and reaching a maximum at about 6 a.m. (Bayliss, 1955). Failure of this nocturnal reduction in hormone secretion might be sufficient to induce hyperadrenalism, and many but not all cases of Cushing's syndrome lose this diurnal variation (Laidlaw *et al.*, 1955; Lindsay *et al.*, 1956). Equivocal hormone findings occur most often in patients with adrenal hyperplasia, and it is in these cases that the response to ACTH stimulation (2 units per hour infused intravenously for six hours) is so helpful (Fig. 3).

Differentiation of adrenopathies.—The distinction between adrenal hyperplasia, adenoma or carcinoma may be made by palpating an adrenal tumour, which usually indicates a carcinoma is present; by finding enlargement of the sella turcica, which suggests a pituitary adenoma and adrenal hyperplasia; or by presacral air insufflation. Often hormone assays make the differentiation.

The excretion of 17-ketosteroids is usually high in adrenal carcinoma, low in adenomas and intermediate in hyperplasia, but the overlap between the three is so great that in individual cases reliance cannot be placed on this differentiation (Forbes and Albright, 1951; Sprague, 1953).

In adrenal hyperplasia the response to ACTH, as measured by glucocorticoid secretion, is greater than normal but minimal or absent in patients with an adenoma or carcinoma. Suppression of the pituitary will reduce the excretion of 17-ketosteroids and glucocorticoids in cases of hyperplasia but not when there is a tumour. Although cortisone or hydrocortisone in high dosage suppresses the pituitary (Jailer *et al.*, 1954), they contribute substantially to the urinary glucocorticoid and 17-ketosteroid excretion; 9 α-fluorohydrocortisone (Cope, 1956) and $\triangle_1$-9 α-fluorohydrocortisone, which suppress the pituitary in a daily dose of 5–10 mg. and 4–6 mg. respectively, are preferred because they do not add significantly to the amount of steroid excreted in the urine.

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Dr. Richard Asher: *Psychiatric Aspects of Cushing's Syndrome*

Mental changes in Cushing's syndrome are very common and a rough estimate from published cases suggests that two-thirds of the patients show some degree of psychiatric disturbance and one-fifth of all cases become psychotic. The commonest change is depression of the mood but severe psychotic changes may occur, with melancholia, retardation and delusions of persecution.

There are three possible causes for the psychiatric symptoms:

(*a*) That Cushing's syndrome is caused by psychic trauma and that the same emotional insult that initiates the endocrine change is also responsible for the psychiatric disturbance. This is an unlikely theory but hard to disprove. There is no good evidence that either Cushing's syndrome or psychoses are caused by psychic trauma; they seem to come "out of the blue".

(*b*) That the mental changes are reactions to the physical stigmata of Cushing's syndrome. As other disfiguring diseases do not show nearly so high a proportion of psychiatric disturbance it seems reasonable to dismiss this theory as improbable.

(*c*) That the mental changes are due directly to the endocrine disturbance. This is the most probable explanation and we have this evidence in its favour:

(i) As it is known that other endocrine diseases produce mental symptoms it seems reasonable to expect that this one might do so.

(ii) Cortisone administration can produce psychiatric changes, so excessive cortisone secretion might be expected to do likewise.

(iii) When the endocrine dysfunction is remedied by treatment the mental changes usually clear up at the same time.

The identification of the hormone responsible for the mental symptoms and the mechanism of their production remain unknown. Attempts to correlate the degree of psychiatric disturbance with steroid levels, electrolyte figures or changes in the cerebrospinal fluid have all proved unfruitful. It is strange that cortisone is noted for producing euphoria whereas hypercorticalism usually produces gloom and despondency, but now cortisone is readily available and less highly thought of, euphoria from its use seems less common.

How do the mental changes respond to bilateral adrenalectomy (which seems the only treatment for Cushing's syndrome)? The number of cases effectively treated and adequately followed up is small, but enough to suggest that the results are good.

Hertz *et al.* (1955) record a young soldier with Cushing's syndrome who ran amok in the guard room with maniacal behaviour followed by an attempt at suicide. Prolonged mental hospital treatment and 26 E.C.T.s had no effect on his apparently schizophrenic psychosis, but when the endocrine component was recognized a dramatic recovery immediately followed bilateral adrenalectomy. Hamm (1955) had 2 cases, both confined to mental institutions with severe symptoms, who made an excellent recovery after operation. Of the 4 severely psychotic cases recorded by Trethowan and Cobb (1952), 3 recovered completely and 1 improved. Other cases with less severe mental symptoms recovered as physical improvement took place. It seems probable that both major and minor psychiatric symptoms clear up completely when Cushing's syndrome is effectively treated.

As an illustration I will describe one of my own cases.

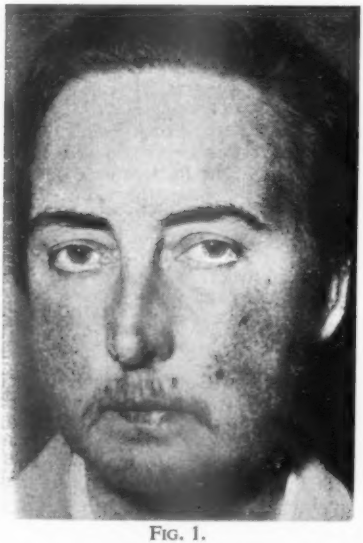


FIG. 1.



FIG. 2.

Mrs. M., aged 40, was admitted to a mental hospital in October 1954 with six months' severe depression. She did not improve with E.C.T., and after one month she was transferred to the Central Middlesex hospital for investigation of a coincidental sciatic nerve palsy. She was mentally too ill to give much history—she was mute and negativistic and usually had to be forcibly fed. Her husband gave a history of her two years' amenorrhœa, rounding of the face, increasing hairiness of the cheeks and chin, 4-st. gain in weight and spontaneous bruising of the legs. These changes were fully confirmed by inspection of the family photograph album. Her face showed the classical changes of Cushing's syndrome (Fig. 1), her urine contained sugar, her legs showed multiple spontaneou

bruises and her blood pressure was 210/140 mm.Hg. Her mental state was even more pathological; most of the time she stayed motionless in deep dejection, mute, miserable and beyond the reach of any kindly or comforting word. Occasionally she would whisper her desire to die; otherwise she was silent and inaccessible.

Total bilateral adrenalectomy was carried out by Mr. Peter Gummer on December 22, 1954. Mental and physical improvement began a fortnight later and continued steadily. Six weeks after operation she was well enough to be allowed home. Two months later she was mentally normal and the change in her appearance was so striking that nurses who had cared for her at the time of operation were unable to recognize her (Fig. 2). Two years after the operation her mental and physical recovery are wholly maintained. Her menses have returned, the hypertension has gone and she is a vigorous, alert and intelligent woman enjoying a happy family life with her husband and children. She takes cortisone 12½ mg. daily.

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Dr. A. Stuart Mason: *Treatment of Cushing's Syndrome by Adrenalectomy*

In April 1953 Dr. Sprague presented to this Section the experience of the Mayo Clinic in the treatment of Cushing's syndrome. He noted the poor prognosis of the disease and the ineffectiveness of earlier treatments. He then reviewed the excellent results obtained by radical subtotal adrenalectomy. This operation is now accepted as the treatment of choice for Cushing's syndrome associated with bilateral adrenal hyperplasia.

Radical resection, or total removal of both adrenal glands has been a feasible operation only since the recent introduction of cortisone and hydrocortisone; experience of the procedure comes slowly because of the rarity of Cushing's syndrome. For these reasons I have attempted a review of the present status of adrenalectomy in Cushing's syndrome by adding my own experience to that of several colleagues.[1]

A valid assessment of adrenalectomy depends on a series of cases which is homogeneous from the clinical aspect, confined to the years when essential hormonal therapy has been available, and with an adequate period of post-operative observation. Therefore, every case included in the series fulfilled the following criteria:

(1) An unequivocal diagnosis of Cushing's syndrome in the absence of an adrenal tumour.

(2) Treatment by adrenalectomy; the first operation being performed between January 1, 1950, and December 31, 1955.

(3) A minimum follow-up period of nine months.

The series comprises 52 cases, the sex and age of the patients being given in Table I. The sex ratio shows a preponderance of females compared to that in other published series (Bishop, 1954) with a relatively large number in middle age. The final clinical assessment is recorded in Table II. The total mortality rate is 25%, but for those patients who survived three months after operation the mortality rate was 9·3% during the period of observation. The results of adrenalectomy are excellent in terms of recovery from Cushing's syndrome and it is unnecessary to dwell on the dramatic clinical change that follows the operation. Only 2 survivors had persistent but non-progressive adrenal hyperfunction and both refused further treatment. However, it is important to realize how many patients have been left with permanent adrenal hypofunction, either from deliberate total adrenalectomy or from atrophy of the adrenal remnant.

The amount of adrenal tissue removed at operation has varied considerably, as shown in Table III. There has been a trend towards more radical removal; 10 of the 11 total adrenalectomies were performed after June 1952 and in 20 of the 26 subtotal adrenalectomies performed since that date less than 16% of adrenal tissue remained; in only 4 of 15 subtotal operations performed before that date was such a small adrenal remnant left.

Some of these operations were performed in two stages; it is advisable to perform the full operation in one stage whenever the patient's condition at operation will allow. Total removal of one adrenal and subtotal resection of the other is preferable to subtotal resection of both adrenals. One patient relapsed some time after resection of both adrenals and it was impossible to know which adrenal should be approached for further operation.

The reason for a radical approach to adrenalectomy is apparent from Table IV. Removal of 50% or less of adrenal tissue failed to control Cushing's syndrome, except in the instance of 2 cases aged over 45 years who also had post-operative deep X-ray therapy to the pituitary. Removal of 90% to 95% of adrenal tissue gave the best results in terms of curing Cushing's

[1]The following contributed material: Dr. R. Asher, Dr. R. I. S. Bayliss, Dr. P. M. F. Bishop, Dr. A. C. Crooke, Dr. R. Fraser, Dr. R. Green, Dr. J. D. N. Nabarro, Professor F. T. G. Prunty, Dr. S. L. Simpson and Dr. A. W. Spence. I am deeply grateful to them and the many other surgeons and physicians who were responsible for the clinical care of these patients.

TABLE I.—AGE AND SEX

Total No. of Cases		52
	Males	11
	Females	41
Age range	Under 25 years	16 cases
	25–34 years	10 ,,
	35–44 years	14 ,,
	45 years or more	12 ,,

Youngest patient = 14 years of age
Oldest patient = 62 years of age

TABLE II.—FINAL CLINICAL ASSESSMENT

Number of patients					52
Deaths within three months of operation					9
Survivors					43
Follow-up period in months	9–18	18–30	30–42	42–54	54–66
Number of patients	10	12	10	3	8

Final assessment	
Alive	39
Adrenal hyperfunction	2
Normal adrenal function	14
Adrenal hypofunction	23

TABLE III.—EXTENT OF OPERATION

Proportion of adrenal removed A	B	52 cases	% adrenal remaining
None	1/2	3	75
,,	5/6	3	58·4
,,	Whole	2	50
3/4	3/4	2	25
Whole	?	1	—
,,	1/2	1	25
,,	2/3	9	16·6
,,	4/5	3	10
,,	7/8	12	6·25
,,	9/10	5	5
Whole	Whole	11	0

TABLE IV.—SUBTOTAL ADRENALECTOMY (SURVIVORS)

% adrenal remaining	No. cases	Disease uncontrolled or relapsed	Adrenal hypofunction
75–50	8	6	0
25–16	9	3	0
10– 5	18	3	9 (+2)*
	35	12	9

*Transient.

TABLE V.—DEATHS

Total 13 (25% Mortality Rate)

Post-operative

(1) Immediate 5
(2) Within three months 4
} 9 { 5 of 39 subtotal adrenalectomies; 4 of 11 total adrenalectomies

Long-term: 4 deaths. Time after operation: 1 year in 3 cases; 5 years in 1 case

syndrome, but there was a significant proportion of cases left with permanent adrenal hypofunction.

6 patients were cured of their original disease by removal of 75% or more of adrenal tissue but relapsed subsequently. The eldest was 37 years of age but the other 5 patients were all under 25. Indeed, 5 of 13 patients of that age group who survived subtotal adrenalectomy relapsed within the period of observation. The average interval between initial operation and relapse was two years. In that time the adrenal remnant had enlarged by four to eight times its original size. This tendency to further adrenal hypertrophy with a concomitant relapse to Cushing's syndrome appears to be confined to the youngest age group.

Of the 12 patients who were not cured of Cushing's syndrome or who subsequently relapsed, 2 died with non-progressive adrenal hyperfunction and 2 survived in a similar state. 8 cases were submitted to further operation, the adrenal remnant being removed in 4 instances and radically resected in the other 4 cases. 2 of the latter patients were cured of Cushing's syndrome but developed adrenal hypofunction, 1 relapsed again and the adrenal remnant was removed, and 1 continued to have a mild degree of adrenal hyperfunction which disappeared spontaneously two years after the second operation.

The 13 deaths occurring in the series are analysed in Table V. There is no mention of post-operative complications which did not prove fatal, but this does not imply that the operation is not fraught with difficulties of management. The appropriate medical care and the problems encountered are very different from those associated with the removal of normal adrenal glands. Cardiovascular disorders were predominant as the cause of death at all times. Death in the immediate post-operative period was due to pulmonary embolus (2

cases), heart failure (2 cases), or cerebral hæmorrhage (1 case). Hypertension played a part in these deaths and in all those which occurred subsequently, with the exception of 1 patient who was mistakenly deprived of his maintenance therapy some weeks after total adrenalectomy. The state of the vascular system is determined by age as well as endocrine factors. The mortality rate in this series was 15% (4 deaths in 26 cases) for those under 35 years old, 22% (3 deaths in 14 cases) for those aged 35–44 years and 50% (6 deaths in 12 cases) for those over 44 years old.

Hypertension may persist after operation and be independent of any abnormal adrenal stimulus. This occurred in 6 patients whose adrenal function became normal after operation. It was also seen in one patient after total adrenalectomy. Continuing hypertension was observed mainly in the more elderly patients with a relatively long history of Cushing's syndrome.

It is difficult to assess the effect of the severity of Cushing's syndrome on the final prognosis, as no case was submitted to adrenalectomy unless the disease could be termed at least moderately severe. The age of the patient and perhaps the duration of the disease appear to be the most important factors in final assessment. The influence of deep X-ray therapy as an adjuvant to adrenalectomy was not ascertained fully as only 6 patients were given this treatment after operation. 2 elderly patients with conservative subtotal adrenalectomy may well have been helped by such therapy. 3 of the other patients developed adrenal hypofunction and 1 had a relapse of Cushing's syndrome.

This series confirms the general experience that Cushing's syndrome is cured by removal of at least 75% of adrenal tissue.

These cases also show that:

(1) There is a very narrow margin between removing enough adrenal tissue to prevent relapse and the amount which causes adrenal hypofunction. There is virtually no margin in patients under 25 years of age. In consequence, the grave decision to undertake a total adrenalectomy is advisable in this group, because of, rather than despite their age.

(2) Patients aged over 45 years are more liable than the younger ones to die after operation, particularly after total adrenalectomy. They are also likely to have suffered irreversible damage to the vascular system. Earlier diagnosis is obviously of importance, but, failing this, subtotal adrenalectomy removing 75% of the tissue or even unilateral total adrenalectomy is preferable to more radical operation. Post-operative deep X-ray therapy to the pituitary should be employed.

(3) Patients aged between 25–45 years should be treated by subtotal adrenalectomy, removing 85—90% of adrenal tissue.

(4) At all times the success of adrenalectomy in curing Cushing's syndrome should be measured against the hazards of operation and the dangers of permanent adrenal hypofunction.

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Dr. J. D. N. Nabarro favoured total adrenalectomy for the treatment of florid cases. Subtotal adrenalectomy, as well as carrying a risk of relapse, might be deceptive: although the patient had sufficient adrenal cortical tissue for ordinary activities there might be no reserve for additional stress.

He mentioned a young patient with bronchial carcinoma complicating Cushing's syndrome due to adrenal cortical hyperplasia. The patient underwent total adrenalectomy and was reasonably well one year later; the carcinoma was progressing but at a much reduced rate.

Dr. C. L. Cope said that many people had now encountered cases showing well-developed clinical Cushing's syndrome, in which laboratory tests for adrenal function were normal, or almost so. The first ten cases he had studied all had urinary hydrocortisone excretions above the upper limit of normal, but the hydrocortisone output of the eleventh was normal. The situation now was that adrenal function tests were of confirmatory value in Cushing's syndrome if raised well above normal, but of little or no value when within normal limits.

Adrenal inhibition tests were of no value in establishing the presence of adrenal hypofunction, since both normal and hyperplastic glands could be inhibited. But if, in an ambiguous case, adrenal inhibition could not be clearly produced by a potent steroid like 9 α-fluorohydrocortisone, then there would be greater suspicion of adrenal tumour and the indication for early surgical exploration of the adrenals would be stronger.

Dr. A. W. Spence said that normal adrenal glands were occasionally found in undoubted cases of Cushing's syndrome. The histological appearance of an endocrine gland was no

necessarily an index of the amount of hormone it was secreting. This was certainly true for the thyroid gland and it seemed to be true in the case of the adrenal cortex.

In patients with Cushing's syndrome due to adrenocortical hyperplasia the treatment indicated depended on the severity of the disease. In the incomplete or milder cases the removal of one gland might produce a satisfactory result, although admittedly a relapse sometimes occurred. The effect of irradiation of the pituitary gland had on the whole been disappointing, although in one patient with the complete syndrome, removal of one gland—followed some months later by irradiation of the pituitary—produced a most satisfactory response. In the severer cases the choice of treatment rested between subtotal and total adrenalectomy. Now that cortisone was available he favoured total adrenalectomy for these patients, because with the subtotal operation a relapse might occur. In one of his patients on whom subtotal adrenalectomy was performed, the subsequent relapse was as severe as the original disease and necessitated a further operation to remove the hyperplastic remnant.

This patient became pigmented after the first operation and deeply pigmented after the second. Pigmentation of this type was at first thought to be due to corticotrophin, but later it was shown to be produced by the melanocyte-stimulating or melanophore-expanding hormone. He understood that this hormone was secreted by the pars intermedia. Did this mean that in Addison's disease and in some cases of Cushing's syndrome there was increased activity of the pars intermedia or was the pigment hormone also produced by the anterior lobe?

Dr. A. C. Crooke and his colleagues had been disappointed with subtotal adrenalectomy for Cushing's syndrome because it was difficult to determine how much gland to remove and recurrence of the initial symptoms or the development of adrenocortical insufficiency was common. They had therefore performed total adrenalectomy recently but were anxious about what complications might arise from this procedure.

Four of their patients who had had total adrenalectomy for Cushing's syndrome or for malignant hypertension, and who had been treated with cortisone only in a dosage of from 37·5 to 50 mg. daily, had developed pain in the spine with persistent slight hypercalcæmia of 11 to 13 mg. per 100 ml. plasma. One, a woman aged 37 years, who had severe Cushing's syndrome complicated by malignant hypertension, had her operation on 29.9.55. She was readmitted for study of her calcium balance and was found to excrete a total of 625 mg. of calcium, including 230 mg. in her urine, on a diet containing 100 mg. calcium daily. They suspected that the bone pains and hypercalcæmia of these patients were associated with progressive loss of calcium and osteoporosis as a result of a specific adrenocortical deficiency.

Mr. R. B. Welbourn said that 13 cases of Cushing's syndrome (12 with hyperplastic or hyperfunctioning adrenal glands and one with an adrenal adenoma) had been investigated and treated by Dr. D. A. D. Montgomery and the speaker in the past three and a half years.

In only one, who came to autopsy, was there certain evidence of a basophil adenoma. The ages ranged from 15 to 53 years, and there were 11 women and 2 men in the series. Special methods of investigation included measuring the excretion of: reducing corticoids (Broadbent *et al.*, 1953), which were raised in all of 5 cases; 17-hydroxycorticoids after two days' stimulation with corticotrophin (Reddy *et al.*, 1952), which were raised in 6 out of 9 cases; and 17-ketosteroids, which were raised in 6 out of 11 cases. Pre-sacral insufflation with oxygen, combined with intravenous pyelography and tomography, was used routinely, but gave false positive and false negative results. It was probably of most value in localizing large tumours.

Treatment consisted of irradiation of the pituitary in 2 cases, subtotal removal of a gland containing an adenoma in 1, and sub-total (95%) removal of one gland plus total removal of the other (in 2 stages) in 12 (Welbourn, 1957). Pituitary irradiation produced no benefit and the patients subsequently underwent adrenalectomy. The results of adrenalectomy were as follows:

No. of patients	13
Immediate post-operative deaths	1
Later deaths	2
Complete remission at 1 to 3½ years after op.	10
No. requiring permanent cortisone replacement ...	3

The patient who died post-operatively developed acute peripheral circulatory failure and coma. The circulation responded temporarily to nor-adrenaline and hydrocortisone intravenously, but the coma did not. No cause of death was found *post mortem*.

The non-adenomatous adrenal glands varied in weight from 2·5 to 15 grams and were normal histologically.

The clinical remissions had been striking (Beck *et al.*, 1954) and all the patients now looked normal. The blood pressure had fallen significantly in all but had returned to normal in only 4, namely the 3 youngest and the oldest. 2 patients had generalized Addisonian pigmentation and 2 others had had their adrenalectomy scars pigmented temporarily.

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Dr. Leonard Simpson stated that although the classical clinical picture of Cushing's syndrome was well defined, it was not surprising that there were various deviations, particularly as the hyperplastic adrenal gland could secrete glucocorticoids and androgens in varying proportions. Although a motley of ill-defined clinical material should be excluded, there still remained a number of atypical or incomplete forms of Cushing's syndrome which merited consideration from the point of view of radical therapy, including subtotal adrenalectomy.

As to treatment, subtotal adrenalectomy was effective in a sufficiently high percentage of cases to be regarded as the method of choice, with a mortality near zero. A portion of the adrenal gland could be kept at low temperature for long periods, for auto-transplantation if and when severe chronic adrenal insufficiency resulted (technique of tissue preservation of Rob and Eastcott, 1955). The vicissitudes and vulnerabilities of patients with severe Addison's disease, or with total adrenalectomy, even in the modern cortisone era, led him to the view that total bilateral adrenalectomy was rarely, if ever, justified for non-malignant conditions.

Finally, one of the most severe cases of Cushing's syndrome under his care at St. Mary's Hospital had adrenal glands of normal size and appearance, and of normal weight, and normal histology; and yet the patient made the most dramatic return to normality after bilateral subtotal adrenalectomy by Professor C. G. Rob, and has remained in normal health for some years.

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Dr. O. Garrod drew attention to data which showed how careful one had to be before assuming that the severe electrolyte disturbances sometimes found in Cushing's syndrome were due to increased aldosterone secretion.

Dr. T. M. Chalmers, Dr. and Mrs. J. F. Tait and the speaker had recently studied the steroid excretions in two cases of Cushing's syndrome due to proven adrenal carcinoma. Both patients had severe hypokalæmia (plasma potassiums of 2·7 mEq./l.) and a very low total exchangeable body potassium, 22·3 and 24·3 mEq./kg. respectively (normal range 35–48 mEq./kg.). The daily urinary steroid excretions in the first case were as follows: aldosterone 4 μg., cortisol 1,200 μg. In the second case, before removal of the adrenal tumour, they were: aldosterone 5·8 μg., cortisol 370 μg., corticosterone 34 μg. After removal of the tumour, the plasma potassium having risen to 4 mEq./l. and the exchangeable body potassium to 35·6 mEq./kg., the steroid excretions were: aldosterone 15 μg., cortisol 5·3 μg., corticosterone 4 μg. The normal ranges of steroid excretion for the method used (Ayres *et al.*, 1957) were as follows: aldosterone 5–22 μg., cortisol 13–86 μg., corticosterone 2·2–9 μg.

It would seem, therefore, that the severe electrolyte disturbances in these cases were due not to excessive aldosterone secretion, the output of this "mineralocorticoid" hormone being at the lower limit of normal, but to excessive secretion of one or both of the so-called "glucocorticoids", cortisol and corticosterone, both of which might have powerful "mineralocorticoid" actions in large doses, comparable with the amounts sometimes secreted in Cushing's syndrome. Unfortunately, because the corticosterone excretion was not measured in the first case, it was not possible from this data to assess the relative role of corticosterone in producing these changes.

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Section of Dermatology

President—Louis Forman, M.D., F.R.C.P.

[*April* 25, 1957]

Parapsoriasis

By J. T. Ingram, M.D.

Parapsoriasis is relatively uncommon and the natural history of the disease, often extending to forty or fifty years, is such that no dermatologist has sufficient experience to talk with authority and it is important to pool our knowledge. The fact that parapsoriasis is almost without symptoms and is unresponsive to treatment increases the difficulty in keeping patients under review.

I shall not discuss parapsoriasis en gouttes, also described as pityriasis lichenoides, for we are now agreed that this is a different entity, self-limited, recovering spontaneously and giving rise to no disturbing sequelæ. I intend to mention briefly poikilodermie of Jacobi and the malignant reticuloses or lymphomas. I shall confine my attention in the main to parapsoriasis en plaques and parapsoriasis lichenoide which is the same as parakeratosis or lichen variegata.

Toward the end of last century and the beginning of this, experienced dermatologists in many countries independently described affections which Brocq (1902) believed to be related and which, without prejudice, he gathered into one group on clinical and morphological grounds alone. Because of some resemblance to psoriasis and the lichens he used the term parapsoriasis and we have since added little to our knowledge of these affections. His terminology and classification are universally employed to-day.

His first group was parapsoriasis en gouttes which was clearly identical in his mind with the pityriasis lichenoides chronica of Juliusberg (1899) later enlarged to include an acute and varioliform variant by Habermann (1925) and Mucha and now generally excluded from the field we have under consideration.

His second group, parapsoriasis en plaques, remains distinctive and well established. Generally, however, the eruption, starting on the legs or arms, presents defined, bizarre, macular lesions of a fawn colour with the semblance of scaling. They are fixed and never disappear though they may wax and wane, they may enlarge or more lesions may appear. Parapsoriasis is either symptomless or sensitive to changes or extremes of temperature, giving a sensation of pricking, burning or soreness but not of itching and no desire to rub or scratch. It may improve and temporarily clear with warmth and sunshine or following the application of thorium X. Otherwise the disease is entirely resistant to treatment but the patients are in good health.

Radcliffe Crocker (1905) used the term xantho-erythroderma perstans which is beautifully descriptive.

A variant which Brocq likened to a "leopard skin" shows profuse symmetrical, nummular or oval lesions mostly on the trunk. A small almost guttate form of this type of parapsoriasis may be difficult to differentiate from pityriasis lichenoides and may require prolonged observation before a decision is reached.

There may be less persistent papular lesions with parapsoriasis en plaques. They have been discussed in detail by Civatte (1936, 1951) and they may confuse the issue but they are different from and less lichenoid than the papules of pityriasis lichenoides and do not run the regular cyclical course of the papules of that disease.

Brocq's parapsoriasis lichenoide, described by Unna as parakeratosis variegata and by English authors as lichen variegata, shows a papular, lichenoid and plaque eruption, reticular in a fine or coarse-meshed fashion, scaly and dusky in hue by reason of congestion and pigmentation. Brocq stressed its resemblance to lichen planus; it is not unlike the lichenoid drug eruptions we have seen in recent years from mepacrine. It is more widespread in distribution than parapsoriasis en plaques but equally persistent and fixed and resistant to treatment. It is symptomless or associated with slight discomfort but no itching. It is much less common than parapsoriasis en plaques.

Civatte (1936, 1951) used the term parapsoriasis lichenoide for a type with the more delicate network and atrophy or pseudo-atrophy and the term parakeratosis variegata for the coarser, thicker, more scaling type. These may be confused with poikilodermie of Jacobi which is a finer, macular affection of flaming telangiectatic networks often with atrophy, pigmentation, papules and ulceration closely resembling X-radiation damage and not at all suggestive of lichen planus. Similar changes in the skin are caused by sunlight, X-radiation, heat and cold, drugs, syphilis, infections and cancer where the target organ would seem to be vascular rather than epidermal.

With these two distinctive types of eruption there is little difficulty for the experienced dermatologist but great difficulty arises from the fact that a number of patients present eruptions that are intermediate between these two types, a fact which Brocq himself noted fifty years ago. In addition, the pattern may change slowly over the years so that at one stage the picture presented is typical of one form of parapsoriasis and at others of poikilodermie. In these intermediate cases difficulties arise over the presence of papular elements, the epidermal thickness of lesions, the degree of scaling and the vascularity. In the same patient, some lesions or even parts of lesions may be persistently pale and others bright red, or there may be a follicular stippling of erythema giving an appearance resembling a fading cattle ringworm lesion. These variations are difficult to understand and are not elucidated by histological examination.

Furthermore the leukæmias and malignant reticuloses (the lymphomas) at any stage may produce xerodermatous or erythrodermic states or bizarre erythematous eruptions indistinguishable from intermediate types of parapsoriasis. A retrospective diagnosis of parapsoriasis in a patient now suffering from a malignant reticulosis may very well be correct but is uncertain.

I have recently reviewed the patients I have seen in private practice with parapsoriasis, a total of 30 in a series of 25,000 patients. I believe that these patients would all be accepted by a gathering of dermatologists such as this and I have omitted all cases in which I had any doubts.

I have seen fifty times as many cases of psoriasis and fifteen times as many of lichen planus.

In the 25,000 patients I have also seen 15 with pityriasis lichenoides and 8 with poikilodermie of Jacobi.

Of the 30 patients under review 19 were male and 11 female and the average age of onset was 39 in males and 36 in females. However, while the age of onset varied from 5 years to 80 years the disease rarely started before 30 years of age or after 45.

The average duration in the patients who have come under my care to date is eighteen years but the range has been from one to fifty years. 4 of the 30 patients have not been traced since the war and 3 others have died, 1 from mycosis fungoides and 2 from unrelated natural causes. The remaining 23 patients have been reviewed this year.

Of the 30 patients 5 presented the pattern of parapsoriasis lichenoide (parakeratosis variegata) and the remainder were essentially examples of parapsoriasis en plaques. One of these, in whom the eruption has persisted now for twenty years, is of Brocq's "leopard skin" pattern and a number of the others show intermediate types of lesions.

A point of some interest is that the son of one of my patients with parapsoriasis has also developed the affection. The father, who died from intestinal obstruction at the age of 65 years, had a coronary infarction a few years before his death. He had had parapsoriasis en plaques for forty-five years. The son, now aged 43 and a patient of my colleague Dr. S. T. Anning, has exactly similar parapsoriasis en plaques which has been present twenty-three years. He also had a coronary infarction two years ago.

In 2 of my patients with parapsoriasis en plaques the eruption cleared, in 1, a boy, after eight years and in the other, a female, after nine years. The affection had started in the one at the age of 5 and in the other at the age of 20.

In 4 patients tumours have developed. In 2 the clinical picture was that of mycosis

fungoides, arising twelve and thirty years after the onset of parapsoriasis. One of these patients has died from the disease. In one patient, a man of 81, parapsoriasis has been present for twenty-one years and during the past ten years the patient has produced tumours clinically resembling mycosis fungoides, which have ulcerated and healed spontaneously in the course of one to six months. The fourth patient, a female aged 76, has had parapsoriasis en plaques for forty years. Ten years ago she developed a single large tumour on the forehead which was excised and histologically showed the infiltration of a malignant lymphoma. She has had no further tumours. I have seen this tendency to tumour formation, single or multiple, in other patients without discomfort or other suggestions of grave malignancy and regard it as an indication for conservative treatment.

In my hospital records there are five examples of malignant reticuloses arising in the course of parapsoriasis at intervals of six to thirty years after the onset of the disease. 4 have died from the disease. In my experience such a transition has been more common in the parapsoriasis lichenoide pattern and in intermediate cases approaching this pattern rather than in the pure parapsoriasis en plaques of the xantho-erythroderma perstans type. This is in accord with the view of Lapière (1949, 1956) and others who suggest that the presence of reticulation and telangiectasia forebodes a lymphomatous development. I do not find the incidence of such change as high as Lapière would put it and I think what I have called the simple pattern of parapsoriasis en plaques can be expected usually to run a benign course.

The last observation I would make on my series is on the coincidental association of parapsoriasis with other dermatoses. 4 patients had xeroderma, familial, from birth. 5 others suffered dry eczematous eruptions from various causes which ran courses quite independently of the parapsoriasis. None had psoriasis.

I cannot get figures of the incidence of parapsoriasis in warmer climates but most patients improve in summer weather. One of my patients says that he clears while in South Africa to relapse on his return to this country. Serri (1951) found few cases reported in Italy.

The differential diagnosis is commonly difficult and not readily resolved. The mimicry of parapsoriasis seen in eczema and psoriasis and with some drug eruptions; the fixity of the eruption reminiscent of drug rashes and the similarity of its behaviour to that of xeroderma and other essentially epidermal reactions as pityriasis rubra pilaris are noteworthy.

Are we dealing then with a single disease entity sometimes presenting as a benign dermatological affection, sometimes as a systemic affection? We are familiar with the conception in vascular disease, in lupus erythematosus, sclerosis, tuberculosis, sarcoidosis and the reticuloses. Or are we dealing with a symptom complex that can be provoked by a variety of stimuli but demands a certain predisposition? There is evidence to support both ideas but the latter would seem the more probable.

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Parapsoriasis Lichenoides en plaque, with Necrotic Nodules, showing Features of Poikiloderma.
—L. FORMAN, M.D., F.R.C.P.

D. B., female, aged 55.

History of skin eruption for thirty years and has been under observation for over twenty-five years. It commenced with a generalized irritable erythema which cleared after a few weeks to be followed by a chronic eruption which was widely distributed over the trunk and limbs.

This has shown the following morphology: (1) On the breasts and trunk a network of brownish-yellow papules—"parapsoriasis lichenoides". (2) Brown, non-pruritic slightly

chapped plaques some becoming confluent—"parapsoriasis en plaques" (Fig. 1). (3) Necrotic nodules healing with scarring. (4) Darker brown, scaling, lightly infiltrated plaques on the buttocks and abdomen, with periods of oozing, healing with pigmentation, dilated capillaries, and slight atrophy recalling the changes of "poikiloderma" (Fig. 2).



FIG. 1.—Parapsoriasis en plaques.



FIG. 2.—Plaque scaling, lightly infiltrated, pigmented with dilated capillaries, of "poikiloderma". Network of linear papules, parapsoriasis lichenoides.

Sections of scaling plaque on thigh (1932): Acanthosis and parakeratosis intra-epidermal vesicles, infiltration of upper dermis with lymphocytes.

Section of nodule: Dense infiltrate of papillary and subpapillary layer of cutis with an infiltrate of plasma cells, lymphocytes, endothelial cells with hæmorrhage.

Treatment and progress.—During 1938, thorium X 500 e.s.u. in spirit was painted on different areas, amounts used 1 c.c. to 4 c.c. at each treatment, 8 treatments in all being given with considerable improvement.

April 25, 1957, lichenoid papules are to be seen on the breast with slight pigmentation. Superficial plaque, brown, non-infiltrated on the right chest (*cf.* parapsoriasis en plaques). A scaling patch on the right thigh darker in colour and slightly infiltrated.

Comment.—There are several questions which remain to be answered. Thus, do parapsoriasis lichenoides, parapsoriasis en plaques, and retiform parapsoriasis exist as entities, morphologically pure, unchanged and innocent? This cannot be certain in view of the very long prodromals of mycosis fungoides. However, in this case with a duration of thirty years, and in another similar case with a duration of twenty-six years, the course appears to be relatively benign. Both cases have responded favourably to thorium X in that a considerable resolution of affected skin has been maintained. The changes of poikiloderma, with erythrodermia, atrophy and skin hæmorrhages may also be long standing but may terminate with malignant tumours. One case of mine developed after twelve years a reticulosarcoma with a histology resembling that of Hodgkin's disease (*Proceedings of the* 10*th Int. derm. Congr.*, London, 1952, p. 535).

Another case was reported by Dr. G. B. Dowling and Dr. E. Waddington (*Proceedings of the* 10*th Int. derm. Congr.*, London, 1952, p. 487) of poikiloderma atrophicans vasculare with a duration of twenty-five years before the onset of mycosis fungoides.

Again, does the skin reaction lead to continued stimulation of the reticulum elements causing eventually an uncontrolled metaplasia? It can be argued, however, that the reticulum changes are primary, the skin reaction being an expression of a response, beneficent in nature, eventually breaking down and allowing the reticulum to become malignant.

Lastly, should our attack on parapsoriasis and poikiloderma be more active, without awaiting the tumour stage, using all the methods available, including thorium X, beta rays, Grenz rays, &c.?

(To be continued)

Section of Proctology

President—RONALD W. RAVEN, O.B.E., T.D., F.R.C.S.

[*November* 14, 1956]

Liver Surgery in Relation to Diseases of the Colon and Rectum

PRESIDENT'S ADDRESS

By RONALD W. RAVEN, O.B.E., T.D., F.R.C.S.

THE relationship of the liver to diseases of the colon and rectum is a subject of academic and practical interest to surgeons. In a number of these diseases there are serious changes in the liver and the assessment of its condition is essential. Our knowledge of the behaviour of the liver under various circumstances has been enriched by the latest methods of biophysical and biochemical investigation.

STRUCTURE AND FUNCTION

Since the detailed account by Bradley (1908) of the morphology and development of the liver an extensive literature on this subject has been built up. Electron microscope studies demonstrate the details of this lobulated compound tubular gland and unveil the structure of its polyhedral cells. It shows the protoplasm with its mitochondria, ergastoplasm and inclusions of glycogen, fat and protein witnessing to the intensive metabolic activity within the cells. Other features include the large-sized nuclei, the quantity of nucleoprotein contained within the distensible nuclear membrane and the fine network of chromatin granules (Figs. 1, 2, 3).

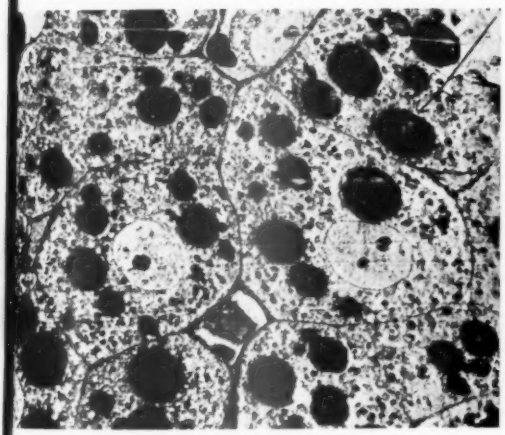


FIG. 1.

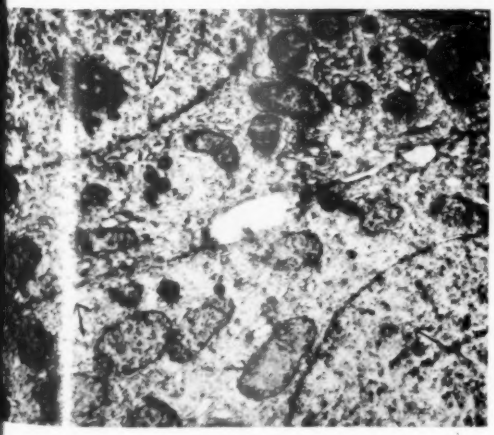


FIG. 2.

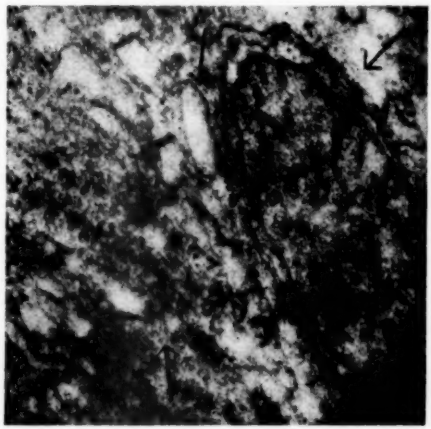


FIG. 3.

FIG. 1.—Electron microscope study of rat's liver showing the general arrangement of the cells and a large number of lipid granules in the cytoplasm (arrowed). ×1,250. (Courtesy of Dr. Mercer).

FIG. 2.—Electron microscope study of rat's liver showing only a part of two cells; the cell membranes are seen running obliquely down the centre and parts of the two nuclei in the corners (arrowed). Mitochondria with their characteristic internal structure are seen in the cytoplasm. ×6,250. (Courtesy of Dr. Mercer.)

FIG. 3.—Electron microscope study of rat's liver showing only a small area of the cytoplasm of a single cell; on the right there is part of a mitochondrion; a large number of nucleoprotein granules and cytoplasmic membranes are also seen (arrowed). ×37,500. (Courtesy of Dr. Mercer.)

Its functions are many and varied; they include the metabolism of pigments, carbohydrates, proteins and fats. It is an important excretory organ for bile constituents, toxins, drugs, and antibiotics; other functions are concerned with detoxication, storage, regulation of enzymes, water, salt, hormones and the blood volume.

Assessment of liver function.—This must be done before operation and is required in many colonic and rectal diseases in order to estimate liver damage and safeguard it from further harm. Important work was done by Maclagan (1956) on liver function tests. The tests required for each patient are chosen according to the clinical condition in the light of the clinician's experience.

Liver function tests.—In the interpretation of the results of these tests it must be remembered that a normal range can be found when severe liver damage is present because the parenchyma has a large functional reserve. Approximately one-tenth of the normal parenchyma is sufficient to maintain adequate function (Bollman and Mann, 1931) and this is demonstrated when large primary and metastatic tumours are present.

In the conservative treatment of ulcerative colitis a group of tests is done at intervals, and evidence of increasing liver damage influences the decision to carry out surgical treatment. In patients with liver metastases, extensive liver damage as shown by a group of tests may exclude the necessity for an exploratory laparotomy. This group includes a positive urinary urobilinogen, retention of bromsulphthalein and alkaline phosphatase raised above 13 units.

Liver biopsy has provided information about liver diseases, and corrected erroneous conceptions; it has influenced the treatment of certain conditions and helped with the prognosis. For example, Himsworth (1950) stated that in fibrotic conditions of the liver an exact diagnosis can be a decisive factor in lengthening a patient's life provided the appropriate treatment is given. Liver biopsy is performed at laparotomy, by needle aspiration and by peritoneoscopy. I prefer the first when the liver can be inspected and palpated and an adequate wedge of tissue selected and excised (Figs. 4, 5, 6 and 7). Experience is necessary to interpret the histological appearances for they differ from those seen in necropsy specimens. They can differ also in aspiration and surgical biopsies. The following are indications for biopsy:

(1) *To exclude liver disease when liver function tests are abnormal.*—One or more liver function tests can be abnormal when liver disease is absent and this may occur in chronic ulcerative colitis, as shown by this patient:

Male age 38 with severe ulcerative colitis of five years' duration preceded by amœbic dysentery ten years ago. Liver function tests: Serum bilirubin 0·2 mg.%, total serum protein 6·6 grams%, thymol turbidity 5, thymol flocculation 2+, serum colloidal gold 4+, zinc sulphate turbidity 8, ammonium sulphate turbidity 3. Liver biopsy: normal appearance. Operation: total colectomy and anterior resection of rectum with immediate ileo-rectal anastomosis. Post-operative liver function tests: Serum bilirubin 0·1 mg.%, thymol turbidity 3, thymol flocculation 0, zinc sulphate turbidity 6, serum colloidal gold 0.

(2) *To exclude liver disease when the liver is palpable.*—A normal liver is often palpable and an incorrect assumption may be made that it is diseased unless a biopsy is done.

(3) *To confirm liver disease.*—Some liver conditions remain obscure without a biopsy, as in ulcerative colitis, amœbic dysentery, chronic infections, benign and malignant tumours.

Results.—A liver biopsy was considered advisable in 30 of my patients who underwent major abdominal operations. In 12 (40%) the histological appearance of the liver was normal. The abnormalities discovered were generalized fibrosis in 7 (23%), local fibrosis in 3 (10%), fatty degeneration in 6 (20%) and carcinoma metastases in 2 (7%).

The Liver in Diseases of the Colon and Rectum

In view of the intimate vascular relationship between the liver, colon and rectum it is surprising that serious effects are not produced more often in the liver by rectal and colonic disease. Effective immunity against many liver infections may be provided by its rich blood supply.

Hepatic lesions in chronic ulcerative colitis.—These should be recognized so that they may be treated or to safeguard the liver from further adverse effects by surgical treatment of the colitis. In more than 500 patients studied at the Gordon Hospital serious liver lesions were uncommon. Liver function tests were done in about one-half, and approximately one-third of these showed minor deviations from normal, only a small number having severe changes.

The following hepatic lesions may occur: (i) Abscess, single or multiple; (ii) Inflammatory foci. (iii) Interlobular hepatitis. (iv) Hepatic fibrosis. (v) Intrahepatic thrombosis. (vi) Fatty degeneration. (vii) Cirrhosis. (viii) Amyloid degeneration.

(i) *Liver abscess.*—This is rare in contrast to its relative frequency in amœbic infection of the colon. Lansbury and Bargen (1933) reported one case; Elsom and Ferguson (1941)

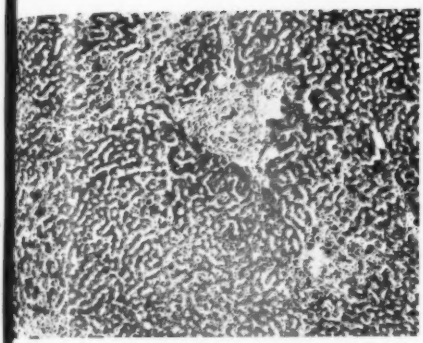


FIG. 4.—Liver biopsy showing normal parenchyma in a case of chronic cholecystitis. ×32.

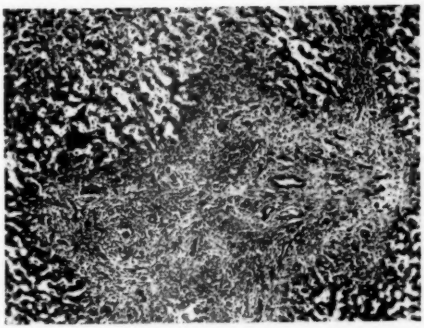


FIG. 6.—Liver biopsy showing the changes of moderately severe biliary cirrhosis—dilatation of biliary sinusoids, peri-lobular fibrosis, lymphocytic infiltration and proliferation of bile ducts. Case of empyema of the gall-bladder. ×32.

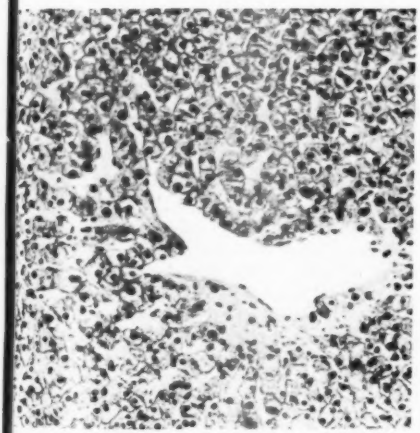


FIG. 5.—Liver biopsy showing a minimal degree of fatty infiltration in a case of chronic cholecystitis. ×125.

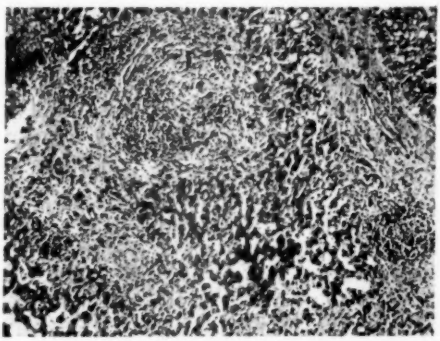


FIG. 7.—Liver biopsy showing the changes of multilobular cirrhosis—patchy fibrosis replacing liver cells with bile duct regeneration. Case of chronic cholecystitis. ×32.

reported a patient who developed it two years after an ileostomy and died; Treusch (1952) gave a detailed report of one patient with a history of four years before she died with abscesses in the upper half of the right lobe. Jones and his colleagues (1951) described one patient who developed pylephlebitis and liver abscesses.

(ii) *Inflammatory foci.*—These are scattered within a lobule, or in the periportal tissue. In the parenchyma they are associated with cell necrosis, but the inflammatory infiltration is predominant. The appearances resemble severe interlobular hepatitis where the lobule is also affected (Kimmelstiel *et al.*, 1952); a similar condition was described by Warren and Sommers (1949).

(iii) *Interlobular hepatitis.*—Inflammatory round-cell infiltration occurs into the interlobular connective tissue with frequent involvement of the adjacent parenchyma where necrosis develops. Later bile duct proliferation and pseudolobulation occur.

(iv) *Hepatic fibrosis.*—A large area of one lobe may be affected without nodular regeneration (Jones *et al.*, 1951).

(v) *Intrahepatic thrombosis.*—Thrombi are found in the hepatic blood vessels; congestion

and necrosis occur in adjacent tissues. Thrombosis of the hepatic and portal veins with massive ischæmic necrosis was described by Kleckner *et al.* (1952).

(vi) *Fatty degeneration.*—This is common and varies in severity; it is probably caused by malnutrition, toxæmia and debilitation (Fig. 8). It was found in 47 (52%) of 91 cases reported by Jones *et al.* (1951). Himsworth and Glynn (1944–5) considered a high fat content of the liver might protect it against necrosis and found that fatty infiltration must be of long duration before fibrosis develops. Kimmelstiel *et al.* (1952) failed to find fat necrosis in severe fatty degeneration. Pollard and Block (1948) stated that fatty changes might cause hepatic insufficiency and cirrhosis. It may be a reversible process.

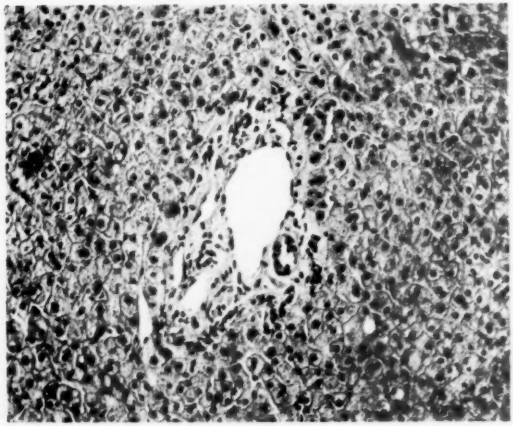


FIG. 8.—Section of liver showing a moderate degree of fatty degeneration and passive venous congestion. Case of chronic ulcerative colitis treated medically for nine years; died from congestive heart failure due to pulmonary embolus, no operation. ×125.

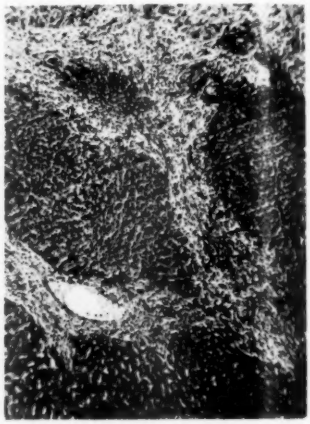


FIG. 9.—Liver biopsy showing multilobular cirrhosis with some regeneration of bile canaliculi. Case of severe ulcerative colitis. ×69.

(vii) *Cirrhosis.*—This is a rare complication. Kimmelstiel *et al.* (1952) found 11 cases in the literature; Jones *et al.* (1951) found 3 cases in 91 cases at necropsy; Tumen *et al.* (1947) reported 5 cases in a series of 151 cases. Kleckner *et al.* (1952) noted it occurred in young adults with colitis for one to sixteen years. Ross and Swarts (1948) considered that anæmia, marked weight loss and protein deficiency cause hepatic insufficiency which, if uncorrected, progresses to fatty degeneration, and serious, irreversible changes. The nutritional factor may be the most important; deficiencies arise from the defective food intake, faulty absorption and protein loss in the rectal discharge. The patients are also subject to a greater risk of serum hepatitis than the general population. Cirrhosis is usually indicated by jaundice, hepatomegaly alone or with splenomegaly, ascites, abnormal liver function tests and biopsy. In the Gordon Hospital series there is only one patient with typical cirrhosis who is under my care:

Female, aged 40, with a history of ulcerative colitis for two years treated conservatively, with tenderness over the pelvic colon and hepatomegaly. Investigations including rectal biopsy, confirmed ulcerative colitis. Patient was treated conservatively for several months and liver function tests were done at intervals with these results:

	Pre-operative			Post-operative	
	12.1.53	10.6.53	6.11.53	24.3.54	8.10.56
Serum bilirubin	0·3 mg.%	1·1 mg.%	0·8 mg.%	0·8 mg.%	0·5 mg.%
Serum alkaline phosphatase	72 units	58 units	56 units	50 units	27 units
Thymol turbidity	3	6	3	5	2
Thymol flocculation ..	0	2	1	2	0
Gold flocculation	0	3	2	1	1
Zinc sulphate turbidity ..	4	7	8	5	3
			Total protein	8·11 gram%	7·5 gram%

The patient's condition gradually deteriorated and on November 16, 1953, a total colectomy and anterior resection of the rectum with an immediate ileo-rectal anastomosis was performed. Liver biopsy showed multilobular fine cirrhosis with some regeneration of the bile canaliculi (Fig. 9). The patient has made a good recovery.

(viii) *Amyloid degeneration* secondary to ulcerative colitis is extremely rare.

Hepatic lesions in amœbiasis.—These have a frequency which is determined by the incidence and efficient control of the primary intestinal infection. A diminution has occurred because amœbiasis is now diagnosed earlier and treated more effectively. De Bakey and Ochsner (1951) reported an incidence of liver involvement in 7·6% to 84·4% (average 36·6%) in necropsy cases, and in clinical cases from under 1% to over 25% (average 8·1%). The abscess is often single (70%) and usually affects the right lobe (85%).

The symptomatology may be entirely hepatic without any symptoms of dysentery. Liver function tests, however, are normal. Radiological appearances include elevation of the diaphragm, consolidation of the right lung base and a pleural effusion. Treatment is with emetine hydrochloride or chloroquine diphosphate and if there is no response both drugs are given together. When an abscess forms, aspiration is required in addition to these drugs and antibiotics and open drainage may be necessary when the wall is very fibrotic. When this type of abscess is in the left lobe of the liver a left hepatectomy is preferable to open drainage.

Pyogenic abscess of the liver.—Gangrenous appendicitis was common before antibiotics were available, and then suppurative pylephlebitis was greatly feared. A liver pyogenic abscess is less frequent, however, than an amœbic abscess. Ochsner *et al.* (1938) reviewed 186 cases of liver abscess during 1928–37, of which 139 (74·7%) were amœbic and 47 (25·2%) pyogenic. At present, cholangitis following common bile duct obstruction is the most common cause and the second most frequent is septicæmia.

Other infections in the portal venous area caused hepatic abscesses in 10·2% of the collected cases and 8·4% of the personal cases in the report of Ochsner *et al.* (1938). These included inflammatory lesions in the terminal ileum, cæcum, colon and rectum. Kramer and Robinson (1926) reported a case of suppurative diverticulitis with pylephlebitis and liver suppuration; a similar case was reported by Whyte (1906). Other primary infective lesions are bacillary dysentery, infected carcinoma of the colon and rectum, regional enteritis, proctitis and infected hæmorrhoids. Taylor (1949) reported the association of regional enteritis and multiple liver abscesses. Alders (1944) reported a male patient who developed a liver abscess after the ligation of internal hæmorrhoids; the abscess burst into the right anterior subphrenic space which was drained with the recovery of the patient.

Metastatic Cancer in the Liver

Approximately one-half of patients who die with cancer have liver metastases. This vulnerability of the liver is due to its position in relation to the portal and systemic circulations, its large size and the composition of its cellular contents. It is affected by many varieties of malignancy including carcinoma, especially of the alimentary tract, pancreas, uterus, breast, bronchus, kidney and adrenals; sarcoma; malignant melanoma; argentaffinoma; neuroblastoma; malignant lymphoma and teratoma.

Portal vein dissemination is the main route of spread from the common sites of malignant tumours in the alimentary tract; those in other sites not connected with the portal system may gain entrance by invading viscera already connected, so that tumours in the ovary, uterus, prostate, bladder, kidneys and adrenals can metastasize to the liver.

Segregation of portal blood in the liver.—It has been suggested that blood from different abdominal organs does not mix in the portal vein and has a lobar distribution in that the left lobe receives a disproportionate amount from the superior mesenteric vein. Clinically one lobe of the liver is found sometimes to contain one or more metastases while the other appears free, this is important in relation to partial hepatectomy. We investigated this problem by injecting 0·1 ml. of ^{24}Na with an activity of 50 μc. into a small tributary of the portal vein and the subsequent passage of radioactivity through the right lobe of the liver was recorded by a collimated scintillation counter placed directly over the centre of this lobe. The counter was then moved over the centre of the left lobe and the injection was repeated into a vein adjacent to the previous one. Our studies have not shown any marked asymmetry in the distribution of portal blood between the right and left hepatic lobes. It cannot be postulated, therefore, that a patient with carcinoma in a certain part of the gastro-intestinal tract is more likely to develop metastasis in one lobe of the liver than the other.

Hepatic artery dissemination.—Metastases reach the liver from primary and secondary tumours in the lung.

Lymphatic dissemination is an uncommon route.

Spread by direct extension of a carcinoma of the hepatic and splenic flexures, transverse colon and other neighbouring sites is common. The primary tumour becomes adherent to Glisson's capsule, an inflammatory reaction develops and malignant infiltration occurs across this adherent area. Liver necrosis then takes place and severe hæmorrhage occurs into the peritoneal cavity, lumen of the stomach or colon and the patient presents as an emergency.

Spread within the liver.—The vascularity of the liver favours intrahepatic spread. Invasion of the right or left main branches of the portal vein causes metastases in the corresponding lobe; when a large radical is invaded a wide segment is affected; invasion of a small venule causes metastases in a localized area. One parent metastasis can therefore disseminate quickly throughout the liver.

Spread from the liver.—Metastases invade the efferent hepatic veins entering the inferior vena cava and are carried to the lungs. The inferior vena cava may be directly invaded (Willis, 1952). The liver acts as an intermediary for pulmonary metastases from primary tumours in the portal venous area. Willis (1952) found 86 of these tumours with hepatic metastases had also produced secondaries in the lungs in 27; in 88 tumours without hepatic metastases, lung metastases were present in only 8.

Incidence and operability of hepatic metastases from carcinoma of the stomach, colon and rectum.—An analysis was made of the relevant details in the case-records of 1,000 patients with primary carcinoma in these sites at the Royal Marsden and Gordon Hospitals; hepatic metastases were considered present in 65 cases on clinical assessment and 157 cases on visual assessment, a total of 222, or 22·2% (Table I).

TABLE I.—INCIDENCE OF HEPATIC METASTASES IN CARCINOMA OF STOMACH, COLON AND RECTUM

Site of primary carcinoma	Clinical assessment		Visual assessment—operation or necropsy	
	Total No. of cases	No. with hepatic metastases	Total No. of cases	No. with hepatic metastases
Stomach	84	27 (32·1%)	276	63 (22·8%)
Colon	37	12 (32·4%)	135	33 (24·4%)
Rectum	102	26 (25·5%)	366	61 (16·6%)
	223	65 (29·1%)	777	157 (20·2%)

The operability was assessed in 157 of the 222 cases with hepatic metastases; operation or necropsy was not done in the remaining 65 cases (Table II).

TABLE II.—ASSESSMENT OF OPERABILITY OF HEPATIC METASTASES IN CARCINOMA OF THE STOMACH, COLON AND RECTUM

Site of primary carcinoma	Total No. of cases	No. of possible cases for partial hepatectomy	No. of cases unsuitable for partial hepatectomy
Stomach	63	14 (22·2%)	49 (77·8%)
Colon	33	10 (30·3%)	23 (69·7%)
Rectum	61	17 (27·9%)	44 (72·1%)
	157	41 (26·1%)	116 (73·9%)

In the series of 157 cases assessed visually for hepatic metastases, 116 cases (73·9%) were considered unsuitable for partial hepatectomy due to extensive liver involvement or other inoperable metastases. This leaves 41 cases (26·1%) with hepatic metastases considered operable for further analysis (Table III).

TABLE III.—DETAILS OF HEPATIC METASTASES FOR WHICH PARTIAL HEPATECTOMY WAS POSSIBLE

Site of hepatic metastases	Total No. of cases 41
Left lobe. Partial hepatectomy performed	5 (12·2%)
Right lobe. Partial hepatectomy performed ..	1 (2·4%)
Solitary metastasis in right lobe	14 (34·1%)
Two metastases in right lobe	2 (4·9%)
Multiple metastases in right lobe	1 (2·4%)
Direct invasion of left lobe	4 (9·8%)
Solitary metastasis in left lobe..	3 (7·3%)
Solitary metastasis—site not stated	4 (9·8%)
Two metastases—site not stated	7 (17·1%)

Summary of statistics.—In a series of 1,000 cases of carcinoma of the stomach, colon and rectum, the incidence of hepatic metastases was 222 cases (22·2%). In the total series a partial hepatectomy was considered possible in 41 cases (4·1%). In the series of 222 cases with hepatic metastases, 41 cases (18·5%) are considered suitable in retrospect for a partial hepatectomy; the operation was carried out in 6 cases (2·7%).

Scheme of treatment of metastatic liver carcinoma.—The management of the following groups of patients is described.

(1) *Metastatic liver cancer from a silent primary tumour.*—The liver symptoms and signs dominate the clinical picture. An exploratory laparotomy and liver biopsy confirm the nature of the hepatomegaly.

(2) *Silent liver metastasis.*—This is a frequent finding when operating for a primary carcinoma of the colon or rectum.

(*a*) *The primary tumour is operable.* When there is diffuse liver involvement the abdomen is closed for the patient's life expectancy is short and palliative treatment is given. When considerable liver parenchyma remains and its function is satisfactory the organ containing the primary tumour is removed. This may retard the progress of the liver disease. When liver metastases are localized in one lobe a right or left hepatectomy is done four weeks after the primary disease is removed.

(*b*) *The primary tumour is inoperable.* Palliative treatment is given.

(3) *Delayed liver metastases after excision of the primary tumour.*—(*a*) *There is no local recurrence.* When clinical examination indicates that one lobe of the liver is affected it is confirmed by an exploratory laparotomy and if there are no other demonstrable metastases or recurrences a left or right hepatectomy is done.

(*b*) *Local recurrence is present.* Palliative treatment is given.

Results of hepatectomy operations for secondary cancer

Left hepatectomy.—A survey of the cases reported, including my own, revealed the following results. A left hepatectomy was performed in 16 patients; 7 patients were alive and well 4, 9, 11, 12, 13, 18 and 20 months later; 1 patient was alive with disease 5 months later; 5 patients died 12, 18, 24, 24 and 24 months later; 3 patients were lost sight of. A local excision of the metastasis was performed in 7 patients; 3 patients were alive and well 6, 8 and 48 months later; 1 was alive with disease 15 months later; 3 patients died 4, 7 and 8 months later.

Right hepatectomy.—A survey of the cases reported, including personal communications and my own, gave the following results. A right hepatectomy was performed in 11 patients; 4 patients were alive and well 12, 18, 18 and 18 months later; 1 patient was alive with disease 6 months later; 2 patients died 4 and 24 months later; 4 patients were lost sight of.

Swellings of the Liver which Simulate Malignant Tumours

Liver swellings occur which resemble malignant tumours and a wrong diagnosis may be made. Surgeons are familiar with "nodules" in the liver which may or may not be metastases. In these cases further investigation should be made. A biopsy of the "nodule" is performed, an operable primary tumour is excised and partial hepatectomy considered later. When a biopsy is not possible and the primary tumour is operable the operation designed to cure the primary disease is performed. The following swellings are considered in this connection.

Liver anomalies.—A good account of these was given by Cullen (1925). A hepatic lobe such as Riedel's may increase in size forming a tongue-like projection from the right lobe which reaches into the right iliac fossa. It is more frequent in females. It may cause intestinal occlusion, as in a case described by Cullen when the hepatic flexure of the colon became adherent to the liver and kinked. Numerous furrows may occur in the liver substance forming intervening lobules which are sometimes pedunculated. Multiple lobes, sessile or pedunculated, may be present in the postero-inferior aspect of the liver.

Liver cysts of various types occur; they include blood vessel cyst, ciliated epithelial cyst, lymphatic cyst and retention cyst.

Hydatid cyst.—According to Dew (1955), 75% of hydatid cysts occur in the liver; the right lobe is affected four times more often than the left. There are two varieties, the first is a unilocular cyst which slowly increases in size, the wall may become fibrosed or calcified and sometimes the cyst is infected and filled with pus. In the second the outer cyst wall is absent and the inner germinative and middle laminated layers invade the liver like a malignant tumour.

Polycystic disease.—A series of 24 proved cases were reported by Comfort *et al.* (1952) in 23 the liver was diffusely affected and in 1 the left lobe was involved. In about half the number of patients polycystic kidneys were present.

Certain chronic infective lesions can be mistaken for metastatic tumours:

Tuberculosis.—Randolph (1930) reported an autopsy on a patient who died after an operation for uterine carcinoma and found many discrete caseous nodules of inactive tuberculosis in the liver which were confirmed histologically. Miliary tubercles occur in the liver in acute miliary tuberculosis and in chronic tuberculosis of lung and bone. Wolf and Flory (1945) reported a case of ileo-cæcal tuberculosis with liver involvement. A tuberculoma is sometimes found forming a caseating swelling, the lesion may be multiple, secondary to pulmonary or abdominal tuberculosis. The swelling may become large and resembles a necrotic tumour or gumma.

Syphilis.—Gumma may be single or multiple in the liver, which is usually not enlarged unless chronic congestion or cirrhosis is associated. Liver nodules may press on the inferior vena cava and the openings of the hepatic veins into it causing ascites and enlarged collateral venous plexuses. Spontaneous healing is frequent leaving marked scarring and nodularity of the liver.

Actinomycosis of the liver is usually secondary to actinomycosis of another organ and the infection reaches it by direct extension from the stomach, duodenum or transverse colon, or through the portal vein from the appendix, cæcum, colon or ano-rectal region.

Benign tumours may be mistaken for metastatic carcinoma:

Hæmangiomata are found more often in the liver than in any other abdominal organ. They are usually small and found in the left lobe; when multiple they cause nodularity of the liver. They are red-purple, rarely protrude above the surface and are compressible unless calcified.

Adenoma is not rare; it may be asymptomatic and discovered at laparotomy, or it may cause an upper abdominal swelling which presses on, or displaces, neighbouring organs and structures. Its consistence varies from soft to hard and it may be single or multiple (Schrager, 1937).

Connective tissue tumours comprise fibroma, lipoma, leiomyoma and myxoma; they are usually small.

Malignant lymphoma often affects the liver; the extent and nature varying with the type of lymphoma. Sometimes discrete nodules are found which simulate metastatic carcinoma, especially in lymphadenoma and reticulum-cell sarcoma.

Nodules of regenerative hyperplasia of the liver were reviewed by Begg and Berry (1953) when they collected 29 cases from the literature and added 4 more. The nodules were pedunculated (19 cases) or clearly delineated from normal tissue (14 cases); the majority had a nodular surface. Histological examination revealed a pattern usually associated with post-necrotic cirrhosis or subacute hepatitis.

Focal hepatic cirrhosis occurs in both sexes at any age and the lesion is usually solitary, but multiple nodules occur which vary in size from a few millimetres to several centimetres. It is often asymptomatic and found at laparotomy when it must be distinguished from primary or metastatic liver cancer. Benz and Baggenstoss (1953) found 34 cases at necropsy comprising 40 nodular lesions. The nodules were usually subcapsular, hard and in the right lobe.

Biopsy of liver "nodule" is frequently necessary to determine its true nature. When the primary tumour is in the pelvic colon or rectum and the abdomen is opened through an infra-umbilical incision visualization of the liver is not possible. In these cases an aspiration-biopsy is done by the method of Pack and Brasfield (1955); the surgeon's right hand is introduced through the wound to identify the "nodule" in the liver so that an assistant can introduce an aspiration needle through the parietes which is then guided by the surgeon into the "nodule".

The Malignant Argentaffinoma Syndrome

Cassidy (1930) described an association of symptoms and signs in a young male patient with an abdominal tumour and liver metastases who experienced a peculiar flushing of the skin of his face and developed pulmonary stenosis. A description of the symptomatology of a malignant argentaffinoma of the small intestine with liver metastases was given by Thorson *et al.* (1954). An argentaffinoma can occur anywhere in the gastro-intestinal tract and up to 1950 approximately 60 cases had been reported in the rectum (Raven, 1950; Thorson *et al.*, 1954).

Clinical groups.—(1) In some patients the tumour is an incidental finding, as in the appendix.

(2) In other patients the symptoms are abdominal or rectal, depending on the site of the primary tumour.

(3) Metastases usually occur in the regional lymph nodes and liver and the general effects are seen of 5-hydroxytryptamine secreted by the hepatic metastases which passes into the blood without being converted by the liver into the inactive metabolite 5-hydroxyindole acetic acid. The release of large amounts in the body produces effects resembling those of histamine release including a fall in blood pressure, dyspnœa and flushing of the skin of the neck.

The following case record demonstrates the value of colonic and hepatic surgery in the treatment of this syndrome. A patient had a carcinoma of the cardia and lower œsophagus infiltrating the left lobe of the liver which I treated by surgical excision. In the portion of liver removed there was a metastatic nodule of argentaffinoma and at a subsequent operation two primary argentaffinomata, and a metastatic lymph node, and several liver metastases were excised by a partial enterectomy, right hemicolectomy and partial right hepatectomy (Fig. 10).

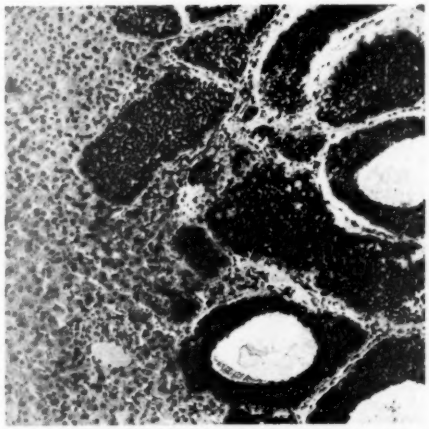


FIG. 10.—Section of liver showing a metastasis of argentaffinoma. ×56.

HEPATECTOMY

History.—The development of hepatectomy operations during the nineteenth and twentieth centuries is divided into two periods.

First period.—Segmental resections of the liver were performed with intrahepatic ligation of blood vessels, and considerable ingenuity can be discerned in the technique employed. The end-results of the *nineteenth century* were generally favourable for benign tumours, but much less satisfactory for malignant tumours. Local recurrence or generalized metastases occurred frequently several months after operation.

Second period.—Lobectomy operations were performed with extra-hepatic ligation of the main blood vessels and lobal duct (Raven, 1949). During the first forty years of the *twentieth century* partial hepatectomy with intrahepatic ligation of the blood vessels was performed with great frequency. The technique of left hepatectomy with extra-hepatic ligation of the main blood vessels and bile duct of the lobe was described independently by Pettinari (1947) and by Raven (1949). This technique was applied to right hepatectomy which was performed by Lortat-Jacob and Robert (1952).

DEFINITIONS OF PARTIAL HEPATECTOMY

Wedge resection.—A lesion at, or near, the anterior border of the liver is resected by two angular incisions. *Elliptical resection.*—A lesion superficial in the substance of the liver is resected by an encircling incision. *Transection.*—Part of a lobe is excised by an antero-posterior incision through its substance. *Left hepatectomy.*—A left subtotal or total lobectomy is performed; in the latter operation the caudate lobe is included. *Right hepatectomy.*—The right lobe is removed.

Combined operations.—(1) *In 1-stage:* hepato-gastrectomy; hepato-œsophago-gastrectomy; hepato-cholecystectomy; right hepato-hemicolectomy. (2) *In 2-stages:* right or left hepatectomy following a left hemicolectomy or an abdomino-perineal excision of the rectum.

Principles of Technique

Left hepatectomy (Raven, 1949).—The abdomen is opened through a transverse incision made half-way between the umbilicus and ensiform cartilage which commences 5 cm. to the right of the mid-line and ends at the left costal margin; a second incision is made at a right angle from this transverse incision upwards in the mid-line to the base of the ensiform cartilage. The left lobe of the liver is mobilized by dividing the left lateral, left coronary, longitudinal and round ligaments; the latter is ligated before division. The left lobe is now retracted to the right and the left branch of the portal vein, left hepatic duct and the left branch of the hepatic artery are ligated and divided.

There are usually three main hepatic veins from the posterior aspect of the liver which join the inferior vena cava in the posterior hepatic groove. One vein passes from the right lobe and another from the left lobe, which open obliquely into the inferior vena cava; the third vein is from the middle of the liver and spigelian lobe and it pursues a straight course to join the main vein. The left and middle veins are ligated and divided.

To remove the left lobe, an oblique antero-posterior incision is made with the diathermy knife from the attachment of the round ligament to end posteriorly immediately to the left of the right hepatic vein joining the inferior vena cava. The raw area of the right lobe is peritonealized by covering it with peritoneal folds derived from the divided liver ligaments. The peritoneum covering the hepatic artery, common hepatic duct and portal vein is sutured. The wound is closed and a soft rubber tube is placed in position to drain the region of the divided liver.

Right hepatectomy (Raven, 1947; Lortat-Jacob and Robert, 1952; Pack and Baker, 1953).—The same technical principles are applied to this operation. The abdomen is explored through a right paramedian incision which is then extended into the pleural cavity through the right eighth intercostal space. The right leaf of the diaphragm is divided radially towards the inferior vena cava. The right lobe of the liver is mobilized by ligating and dividing the round ligament, dividing the longitudinal and right coronary ligaments. The cystic duct is then ligated and divided; the right hepatic duct and the right branch of the hepatic artery are ligated and divided. The right branch of the portal vein is shorter and broader than the left branch and must be exposed anteriorly, the liver is then rotated to the left so that this vein can be exposed also posteriorly; it is then ligated and divided. The inferior vena cava is then exposed and the two hepatic veins from the right lobe and middle part of the liver and any smaller veins are identified, ligated and divided. The left hepatic vein is seen and preserved. The right lobe of the liver is then removed by dividing the liver with the diathermy knife antero-posteriorly immediately to the left where the main right hepatic vein joins the inferior vena cava.

Any bleeding vessels and small bile ducts in the divided left lobe are transfixed and the bare area is peritonealized using the divided hepatic ligaments. The peritoneum covering the hepatic artery, common hepatic duct and portal vein is sutured. The diaphragm is then sutured and the right pleural cavity is closed with underwater drainage; a soft rubber tube is placed in position to drain the region of the divided liver and the abdominal wound is closed.

Effects on the Liver of Operations

Experimental work has shown morphological and biochemical changes in hepatic cells. Cole and Leuchtenberger (1956) compared the histological appearances in dogs pre- and post-operatively. In the pre-operative liver the chromatin in the nuclei was finely granular and evenly distributed, but in the post-operative liver it was coarse, coalescent, distributed irregularly, and large rarefied areas were present. The nucleoli after operation became larger with irregular borders. The changes were most obvious three to six hours after operations and no appreciable differences were seen three or four days later, and the severity of the operation did not influence the effects. These workers also found an increase in the tyrosine content of the cytoplasm three hours following operation, but no change occurred in the desoxyribonucleic acid in the nucleus. The interpretation of these results is not yet clear; they may indicate increased protein synthesis by the liver or the presence there of the products of increased protein catabolism.

Clinical work also demonstrates certain changes. In 11 patients undergoing a major abdominal operation serial liver function tests were done before, at the end of the operation and three days later. In 9 patients the serum bilirubin rose as much as six times its pre-operative level; greater increases were found in those given blood transfusions. No changes occurred in the flocculation tests, and in 2 patients a mild fall occurred in the total serum

proteins. Tagnon *et al.* (1948) carried out liver function tests in 20 patients immediately after an extra-abdominal operation and found a significant increase in bromsulphthalein retention in 14. The effects of giving ether and Pentothal-sodium were not important. Geller and Tagnon (1950) investigated changes in the tests in 33 patients after major abdominal operations; in 17 of 22 there were abnormalities in the bromsulphthalein test; in 14 of 22 in the cephalin flocculation test, and 24 of 33 patients had abnormally high serum bilirubin for several days. There was an increased production of bilirubin and post-operative impairment of liver function with blood transfusion. Keeton *et al.* (1948) found the maximum excretion of urinary urobilinogen occurred on the third day after herniorrhaphy and cholecystectomy which returned to normal by the sixth day.

Causes of Liver Damage in Operations

These include trauma, shock, anæsthesia and inanition. Anoxia in anæsthesia or shock causes parenchymal damage. French *et al.* (1952) observed no difference between the effects of ether and cyclopropane; Geller and Tagnon (1950) found no changes in the liver function tests with nitrous-oxide gas, ether and oxygen, spinal anæsthesia alone and combined with Pentothal Sodium. Keeton *et al.* (1948) found that post-operative inanition affected liver function and a high caloric diet containing 2·6 grams protein per kg. resulted in a positive nitrogen balance.

The effects of liver abnormalities can be greatly increased by even minor operations and may cause death. For example hepatic coma may develop in twenty-four to forty-eight hours after a paracentesis. This procedure is usually necessary to relieve dyspnœa or severe abdominal distension, but it must be done with caution; when severe liver damage is present the operation is done in stages. Severe gastro-intestinal hæmorrhage is an important cause of hepatic coma; the retained blood may release ammonia. The hæmorrhage and shock are controlled and when practicable the blood is removed from the colon by an enema.

Other precautionary treatment with liver damage.—Bed-rest is essential when the liver is tender, jaundice is present and liver function tests very abnormal. Protein deficiencies are rectified as much as possible. Avoid acute infections, maintain the urinary output and do not overload with fluid when oliguria is present and not associated with dehydration. Caution is necessary in the use of ammonium salts as diuretics, of sedatives, analgesics and hypnotics. Morphine is contra-indicated for it is conjugated in the liver before excretion; pethidine can be given. Choose the barbiturates with the greatest renal excretion, namely barbital and phenobarbital, and carefully grade the dosage. Avoid paraldehyde and chloral hydrate; bromides can be given. Fluid intoxication and dehydration should be prevented and the electrolyte and water balances maintained. The diet should be rich in protein, such as meat and fish, and 150 grams are taken with 350 grams carbohydrate, and 70 grams of fat. Vitamins and liver extract are included but salt is excluded when ascites or œdema is present.

Liver Regeneration following Hepatectomy

The liver possesses good power of regeneration; Schroeder (1906) quoted Ponfick who removed three-quarters of the organ and found it regenerated to four-fifths of its normal weight, and in some cases it regained its full weight. Localio and Saltz (1950) described the regeneration of the liver in a patient after massive mechanical destruction. Pickrell and Clay (1944) stated that large areas of the liver can be destroyed by disease or removed surgically and regeneration occurs promptly and almost completely.

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Section of Obstetrics and Gynæcology

President—R. A. BREWS, M.D., M.S., F.R.C.S., F.R.C.O.G.

[*February* 22, 1957]

DISCUSSION ON THE ÆTIOLOGY OF PRE-ECLAMPSIA

Professor J. C. McClure Browne:

Placental Ischæmia is not an Ætiological Factor in Pre-eclamptic Toxæmia

No two speakers on the subject of pre-eclamptic toxæmia will present the same points of view, because there are as many theories on this subject as there are obstetricians.

My interest in pre-eclamptic toxæmia and its ætiology is, I think, clearly an inherited one, and obviously it must be due to some hitherto undescribed dominant gene. Then in 1946 I was fortunate enough to come under the influence, first at Hammersmith and later in Edinburgh, of Professor Robert Kellar, who in his own inimitable way goaded me into taking a more active interest in this particular problem. About that time, too, the work of Beker (1948) and of Bastiaanse and Mastboom (1949) revived attention on the placenta as the supposed starting-point of the chain of events which culminates in eclampsia. As far back as 1914, Professor James Young—my predecessor at Hammersmith Hospital—had postulated that the red infarct which could be, and still can be, demonstrated in cases of eclampsia was the site of origin of chemical substances which initiated the whole syndrome. Ernest Page (Ogden *et al.*, 1940), too, had shown that partial occlusion of the aorta in the pregnant bitch resulted in a rise in systemic pressure. From these observations, and others, arose the idea that placental ischæmia existed in pre-eclamptic toxæmia, and, as with so many matters in obstetrics, once it had been postulated, it became apparently accepted as a fact, and on this supposed fact new theories of the ætiology of pre-eclamptic toxæmia were put forward.

If one accepts that placental ischæmia will indeed cause a rise in systemic blood pressure, then it is logical to suppose that pre-eclamptic toxæmia will develop in conditions where the pregnant uterus is subject to over-distension; conditions such as hydramnios, twins and, in some cases, in the primigravida. Professor K. Franklin and Mr. Sophian have shown that distension of the pregnant rabbit uterus will cause a renal cortical ischæmia which could be held to account for the occurrence of albuminuria. Recently, however, McGaughey *et al.* (1956) in experiments on the dog have failed to show that a specific utero-renal reflex exists.

Up till 1948, though there was evidence to suggest that placental ischæmia might have an important role to play in the ætiology of pre-eclamptic toxaemia, nobody had shown that such a condition actually existed, and it seemed to me vital to prove or disprove this. To do this Veall and I considered that it was important that the placenta should be studied *in situ* before the fœtus was delivered, and indeed before the uterus was opened. The first problem was to find the placenta under these conditions, and for this reason we developed a method of locating it using tracer doses of radio-active sodium (Browne, 1951). The method (Browne and Veall, 1953), though established purely for this experimental purpose, has important clinical applications in the exclusion of placenta prævia as a possible cause of antepartum hæmorrhage, and is in general use to-day at Hammersmith for that purpose.

In cases where we found that the placenta was situated anteriorly it was possible to inject a tracer dose of ^{24}Na into the chorio-decidual space, and to record the time taken for it to be cleared by the maternal placental circulation In the normal case—that is to say the woman without pre-eclamptic toxæmia or hypertension—between 38 and 40 weeks the mean half-period for clearance was 21 seconds. In cases with pre-eclampsia the mean half-period was 65 seconds, more than three times as long, showing clearly that in pre-eclampsia a true placental ischæmia existed. However, in cases of essential hypertension, even mild cases, where the hypertension had antedated the pregnancy, the same degree of ischæmia was found. We concluded therefore that the placental ischæmia was the result and not the cause of the hypertension which is one of the cardinal features of pre-eclamptic toxæmia. We were astounded at the marked reduction in maternal placental blood-flow that occurred when hypertension was present, and at first refused to accept it as valid. However, careful review of our methods and results showed that we should indeed accept it. Subsequently, Morris *et al.* (1955) at University College Hospital adapted our method to study the clearance of radio-active sodium from uterine muscle, and showed that there, too, the same reduction in blood-flow as evidenced by prolongation of clearance time existed. Walker and Turnbull (1953), working on the other side of the placental membrane, found that in these conditions there was evidence of fœtal anoxia, in that the concentration of hæmoglobin

in the fœtal blood was raised. Neither Morris nor I found any diminution of tissue clearance in striated muscle.

The existence of this placental ischæmia in cases of hypertension, whether essential or pre-eclamptic in origin, explained many things. For example, it explained why the baby tends to be small in cases of essential hypertension and the serious significance of hypertension in association with post-maturity in which placental insufficiency is also a feature (Browne, 1954). It explained, too, many of these cases of intra-uterine death in the last few weeks of pregnancy, when only a mild hypertension was present.

This clear evidence, therefore, that hypertension causes placental ischæmia, suggests that the uterine tension theory for the origin of pre-eclampsia is wrong. We are told by the exponents of this theory that the tension of the primigravid uterus, or the presence of twins, or hydramnios, conditions frequently associated with pre-eclamptic toxæmia, produces a placental ischæmia and if the intra-uterine tension be reduced—for example, by rupturing the membranes—then the ischæmia is diminished and the toxæmia is immediately improved. But this certainly is not my experience in clinical obstetrics, and I am sure we would all agree that there are many instances of serious deterioration in cases of pre-eclamptic toxæmia after surgical induction has been performed, so that we are compelled on occasion to perform Caesarean section in this particular type of case because of imminent eclampsia.

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Mr. Norman Morris:

The pioneer work of Professor McClure Browne stimulated Dr. Helen Payling Wright and myself to investigate the clearance rate of ^{24}Na from the myometrium. Initially we selected mothers at rest in hospital between 30 weeks and term. A point was chosen on the abdominal wall about 4 cm. below and lateral to the umbilicus. This was infiltrated with between 1 and 2 c.c. of 1% lignocaine. The injection needle was then introduced through this area into the myometrium and 0·3–0·4 ml. of ^{24}Na with an activity of between 5 and 10 μc. was injected (*see* Fig. 1). A Geiger counter was then arranged over this site and the rate of clearance of the ^{24}Na recorded. After correcting our results for the rising background they were then expressed in terms of the time taken for the counting rate to reach half value (Fig. 2). These figures clearly show a reduction in clearance rate and therefore presumably of myometrial blood flow in relation to pre-eclampsia.

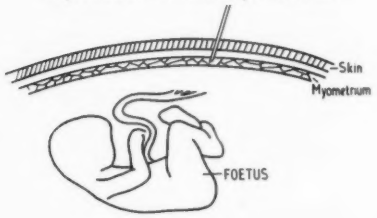


FIG. 1.

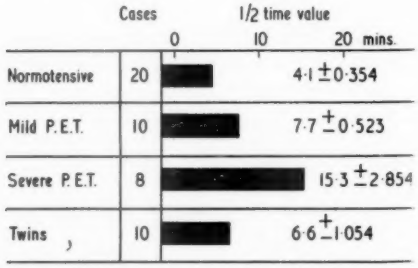


FIG. 2.—Uterine clearance rate of ^{24}Na in pregnanc

Our series was then extended to some 90 cases. In a few we measured the clearanc rate after lowering the blood pressure with protoveratrine and the results are shown i Fig. 3. Lowering the blood pressure appeared to improve the clearance rate.

We then investigated the effect of exercise upon the clearance rate of Na from bot the myometrium and the anterior belly of the quadriceps. For this we devised an Exercycl With the patient at rest an initial clearance reading from an injection into both th uterus and the quadriceps was obtained in a similar way to that already described. Sh

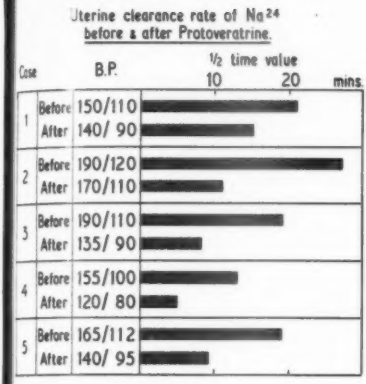


FIG. 3.

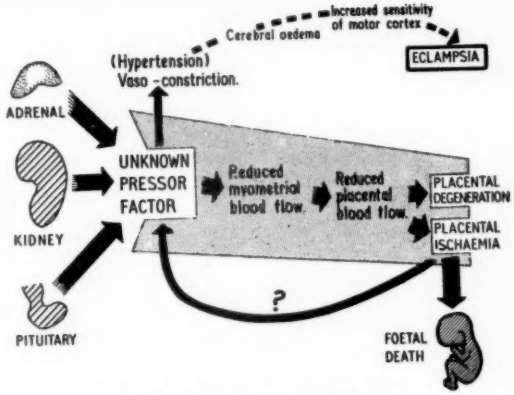


FIG. 4.—Pressor effect in P.E.T.

was then encouraged to use the apparatus; after she had achieved a steady pace for some 5 minutes, she stopped for a few moments just long enough for us to give an injection into the uterus and quadriceps. After this she resumed her cycling for a further 5 minutes. At this point she stopped and was encouraged to relax as much as possible. The results were as follows:

In both groups there was a significant rise in diastolic pressure during exercise. In the 5 minutes following the pressure fell rapidly towards the resting level.

	Resting	During exercise	After exercise
Normals ..	73·3 ± 1·75	85·5 ± 2·22	75·8 ± 2·31
Pre-eclamptics ..	93·3 ± 1·71	98·9 ± 2·53	91·4 ± 2·45

In both groups there was a statistically significant decrease in uterine clearance rate during exercise. This quickly returned to normal within 5 minutes when exercise was stopped.

Uterine clearance rate: Time to half value in minutes.

	Resting	During exercise	After exercise
Normals ..	4·07 ± 0·27	5·43 ± 0·42	3·07 ± 0·43
Pre-eclamptics ..	7·17 ± 0·22	8·75 ± 0·52	6·25 ± 0·53

These results therefore suggest that during exercise there is a reduction in blood flow to the uterus with a quick return after this is stopped. Furthermore it seems probable that this reduction in uterine blood flow is the result of a generalized splanchnic vaso-constriction since in the non-pregnant exercise also reduces the renal blood flow. The actual extent of reduction is possibly governed by many other considerations such as height, weight, skeletal development and the general state of bodily fitness.

It may be of value to consider the possible clinical significance of these findings. It is well established that rest usually helps to prevent deterioration in a case of pre-eclampsia; physical activity appears to have the reverse effect.

The origin of the pressor mechanism is unknown. Mr. Sophian thinks it largely originates from the kidney, others think it may come from the placenta while still others believe it may arise in the adrenal or pituitary. Whatever its origin, we would probably agree that its effect on the uterus and placenta is as indicated in Fig. 4. It can be seen that exercise by intensifying the vaso-constriction will also temporarily exacerbate these changes.

Since physical activity produces a subsequent hypertensive exacerbation of some duration it would appear that the increased splanchnic vaso-constriction provoked during exercise may also have the effect of stimulating or perpetuating the production of the pressor factor from whatever viscera this may arise.

In this way a vicious cycle is established. The blood pressure rises and eclampsia becomes more imminent. The uterine blood flow is progressively reduced. The changes occurring in the placenta are illustrated in Fig. 5. The placental blood flow is impaired and trophoblastic anoxæmia results. This, in turn, may result in irreversible trophoblastic degeneration and infarct formation. These changes may be associated with an intrinsic failure of placental development which sometimes seems to be a related factor in severe early pre-eclampsia.

As term is approached there is a natural reduction in placental function, sometimes referred to as "senility".

As a result of all these changes there is a progressive reduction in placental function and intra-uterine death of the foetus may occur. Rest can only partially reverse this sequence of events and, clearly, to be effective, it must be instituted at a very early stage.

Fig. 6 illustrates the ill-defined frontier between the normal patient and the one with

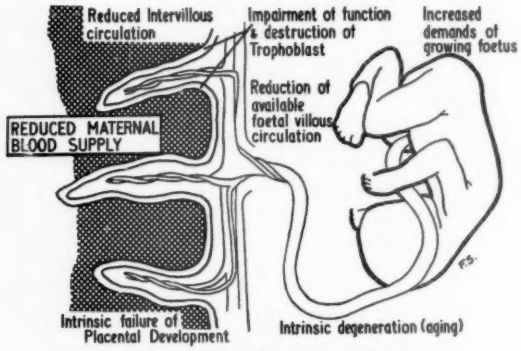


FIG. 5.—Placental changes in P.E.T.

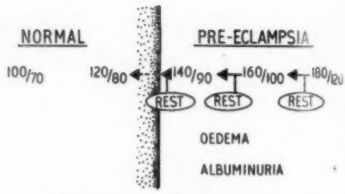


FIG. 6.—The effect of rest on the incidence and severity of P.E.T.

pre-eclampsia. Many of us do not agree regarding the upper limit of the normal blood pressure and we confine our attention to those patients who show indisputable evidence of pre-eclampsia, such as hypertension, œdema, and albuminuria. Our results are good, but many women do progress to moderate or even severe pre-eclampsia before we see them.

I believe that *all* primigravidæ and any other patient thought to be particularly susceptible to pre-eclampsia should be advised to rest as much as possible from 30 weeks onwards. In all probability this measure would completely alter the pattern of severity of pre-eclampsia. The mild cases would occur later, or never at all; the moderate would become mild, and the severe, moderate. In turn the perinatal mortality from this condition should be much reduced.

Mr. John Sophian: *The Cause of Pregnancy Toxæmia*

If patients with incipient or pre-existing hypertension are excluded toxæmia is *never* met with outside primigravidity, hydramnios, concealed accidental hæmorrhage, hydatidiform mole, or multiple pregnancy.

Since "essential" hypertension can possibly occur as a result of a renal mechanism [1], and since renal ischæmia can be held to explain the œdema, hypertension and albuminuria which characterize the toxæmic state [2]—signs entirely similar to those of acute glomerular nephritis, an undoubted renal disease [41]—it is reasonable to infer that a renal ischæmic change occurs in pre-eclampsia. This condition is associated with an increased resistance to stretch of the uterine muscle and such a resistance could be evoked by uterine over-distension; or even normal distension of the primigravid uterus. The utero-renal reflex demonstrated by Franklin and Sophian [3] has shown that by provoking resistance in the rabbit's uterus (by fluid distension) a stimulus is produced causing renal cortical ischæmia. Evidence has thus been produced to correlate these renal changes with toxæmia [4]; further, all grades of renal ischæmic change, and cortical necrosis have been produced by renal nerve stimulation [5], which suggests that anuria can result from a reflex response. Evidence of a utero-renal reflex is provided by the over-distension of the uterus in concealed accidental hæmorrhage causing anuria due to renal cortical ischæmia. It has been shown that removal of the distension-stimulus by rupture of the membranes and interruption of the suggested nervous reflex by splanchnic block [6 and 7] is sufficient to overcome incipient or early anuria. Correlation of the severe cortical ischæmia of anuria with the renal state underlying pre-eclampsia was shown when intravenous saline, mistakenly administered as a therapeutic measure to an anuric, precipitated œdema, hypertension and fits [8]. Albuminuria is always detectable in the earlier oliguric phase and when an excess of salt and water exists in the presence of renal ischæmia all signs of toxæmia are evoked. Pre-eclampsia and eclampsia may also be produced when this sequence is reversed, salt and water retention being preliminarily affected by giving D.O.C.A. and salt, followed by renin [9].

In the pre-eclamptic process there is a great deal of evidence to show that renal ischæmia

is continuing as pregnancy advances, evidence that is derived from the reduced glomerular filtration rate and renal plasma flow figures [10] and from renal biopsies [11]. The signs can also be construed as those resulting from renal ischæmia [12]. It is suggested therefore that the *continuing* ischæmia of the kidney is responsible for the signs of pre-eclampsia. *Sudden* renal shut-down, as evidenced by the development of anuria, has a possible counterpart in the suspension of renal function in the salmon when it changes its river habitat for the sea; and it can be shown that this is entirely due to the presence of salt in the new environment [13]. It should be noted also that the kidney is more prone to an "anuric" shut-down if the liver is damaged [14], and as a corollary, renal damage of an ischæmic type can result from compression of the porta hepatis [15]. The supervention of fits, coincident with severe exacerbation of hypertension, has been seen following prolonged clamping of the remaining renal pedicle, after unilateral nephrectomy; cerebral vascular spasm accompanies this manifestation. Further, these experimental animals, who have been kept on saline, can occasionally develop severe œdema, thus demonstrating the association of œdema, hypertension and fits with ischæmia of the kidney [16]. In the causation of fits, changes in the electrolyte concentration of the plasma have been shown to be responsible [17]. Sodium and chloride concentration of the plasma can therefore be responsible both for a renal shut-down, as in the salmon, and for the production of fits, while salt is necessary for the production of hypertension [18]. Renal ischæmia can cause the retention of salt and water [42] and a 1% reduction of the glomerular filtration rate (G.F.R.) can account for the retention of 10 grams sodium daily—a not inconsiderable amount when spread over the later months of a toxæmic pregnancy when G.F.R. is markedly reduced. Recent work in the experimental animal has demonstrated a reduction of one-third in the G.F.R. during the early periods of uterine distension [19]. Nephron dissections, which help to differentiate purely ischæmic lesions from those in which poisons have been active, clearly indicate that the tubular damage is due to ischæmia in the anuria following eclampsia [20]. All this evidence suggests the presence of renal ischæmia in pre-eclampsia which by producing salt and water retention can be responsible for hypertension, fits and even anuria. Alternatively, the principal effect of renal ischæmia may be directly upon the vascular system, enhancing hypertension and evoking encephalopathy. It has been shown in nephritis that reducing the renal blood flow increases the escape of protein through the glomerular filter by slowing the stream, suggesting that renal ischæmia produces the albuminuria as well [21]. It follows that every sign and complication of toxæmia can be explained by renal ischæmia. Corticoids [22], which are in the main responsible for the shifts of retained water and electrolytes in the body compartments are of secondary importance.

Evidence that the uterine stimulus originates in the resistance to stretch of the myometrium is both direct and indirect. Uterine tone has been shown to be raised in hydramnios [23], in toxæmic pregnancy [24], in concealed accidental hæmorrhage [25] and also in hydatidiform mole in which Acosta-Sison [26] has drawn attention to the association of the height of the uterus with the severity of the toxæmia, an implication of increased regression also present in primiparity indicating increased myometrial tension [37]. Apart from this direct evidence, puncture of the membranes in pre-eclampsia [27] and oliguria [28] is associated with clinical improvement before labour commences, while introduction of a hydrostatic bag for purposes of induction in toxæmia has been observed at least on one occasion to precipitate anuria. It should be added that interrupting the arc of the utero-renal reflex by caudal analgesia has great therapeutic value [29], as has destruction of the nervous pathways [38]. It has been shown, that increased tension of the uterine wall causes a reduced circulation through the myometrium [30] while a noticeably reduced myometrial circulation has been found constantly and continuously in pre-eclampsia [31]. This circulation can also be diminished by exercise [12]. On one occasion in toxæmic pregnancy considerable augmentation of the blood flow through the uterine wall and amelioration of the pre-eclamptic signs were apparent on the death of the fœtus [32]. Presumably this was due to its crumpling, resulting in a reduction of the stretch factor with corresponding diminution of the utero-renal reflex. Prolonged contraction of the uterus during labour has on one occasion been found to coincide with the onset of toxæmia [33]. The adenosine content of the blood in toxæmia, indirect evidence of a heightened uterine tone, has been found to be much higher than in normal pregnancy [34].

Toxins originating from the fœtus or the placenta cannot be responsible for the ætiology, since amelioration of toxæmia results on the intra-uterine death of the fœtus, although it is still retained *in utero*. Such toxæmia can recrudesce at labour when the death of the fœtus and placenta exclude the renewed manufacture of such hypothetical substances [4]. Nephron dissections of the kidney of patients with eclamptic anuria do not show any toxic effect on the tubules [20]. Neither is it reasonable to assume that toxin production is exclusive to first pregnancies alone; indeed no toxin has yet been found.

Examination of the hypothesis that hormones are responsible for pre-eclamptic signs suggests that such substances play no primary part in production [35]. An antigen reaction can be excluded, as its incidence should become more pronounced in later pregnancies, whereas toxæmia is a disease of the primigravid. Dietetic theories fail to appreciate the effect of salt which aggravates the condition.

Certain criticisms have been levelled against the thesis put forward here viz.:

(1) It cannot explain postpartum eclampsia. But Franklin has found renal ischæmia particularly marked during labour and coinciding with the postpartum contractions of the uterus.

(2) It has failed to produce toxæmia experimentally. This work was carried out with rabbits and the rabbit's uterus cannot resist stretch for a period long enough to allow pre-eclampsia to develop; neither has the animal suitable suprarenals, a fact indicated by the D.O.C.A. priming necessary to provoke eclampsia [9].

(3) A denial of the existence of the "dual" [Trueta, 39] circulation in the kidney on which the thesis is based. This criticism originated because current biochemical interpretations of renal hæmodynamics were only valid for a single renal circulation. However, Pappenheimer [36] claims that a dual circulation must be postulated to explain the filtration fraction and the less than 100% extraction ratio that prevails.

It is again postulated that the ætiology of toxæmia is to be found in the resistance of the myometrium to stretch provoking renal ischæmia. This, if pre-existent in essential hypertension or brought about by the utero-renal reflex or exercise [40] explains the reduced uterine blood flow it effects.

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[*May* 24, 1957]

DISCUSSION ON PREVENTION OF ECLAMPSIA

Professor G. Gordon Lennon:

Induction of Labour in Pre-Eclampsia and Eclampsia

I. *Indications:*

(1) To cure eclampsia after control of fits

(2) To cure toxæmic accidental hæmorrhage

(3) To cure pre-eclampsia (To prevent eclampsia and/or accidental hæmorrhage).

A. Acute case. (*a*) Rising blood pressure despite treatment. (*b*) Increasing albuminuria.

B. Acute on chronic case. (*a*) Rising blood pressure. (*b*) Accidental hæmorrhage.

C. Chronic case. (*a*) Maintenance of blood pressure at toxæmic level (140/90 or above) under treatment and gestation at least of 36 weeks' duration. (*b*) Continuing slight or recurrent slight albuminuria. Slight albuminuria not exceeding 14 days' duration.

(4) To avoid placental insufficiency. Cured pre-eclampsia however mild or recurrent; gestation at least of 36 weeks duration.

Before considering relevant points I should like to emphasize that from 1951 to 1956 I have taken 130/80 as the *upper* limit of normal blood pressure, a level indicated for many years by Professor F. J. Browne. Any woman who has started pregnancy with a blood pressure of this level, or below, and who rises to a level of 140/90 I have regarded as toxæmic. In 1951 the severity of toxæmia in my wards was high. An attempt, therefore, had to be made to impress general practitioners with the importance of the condition in its early stages by admitting to hospital those patients with a blood pressure of 140/90 and no other signs of toxæmia. In addition, visiting lecturers helped the crusade including Dr. Hamlin and Professor Bruce Mayes from Sydney who have done so much to teach us the intensity of pre-natal care required in the management of toxæmia. In this connexion I would like to mention another from Sydney, Mr. T. Dixon Hughes lately deceased, who was the prime instigator of the wonderful results achieved at Crown Street Hospital. He showed before anyone else that in practice, albeit his private practice, eclampsia need not occur, and I wish to record this small tribute to him. Latterly in Bristol, patients with early evidence of toxæmia have not been admitted to hospital, but have been put to bed at home with daily supervision by midwives and general practitioners. Since I believe that fulminating eclampsia represents inadequate pre-natal care, general practitioners have been asked to see that patients with a blood pressure which does not settle within forty-eight hours after rest in bed at home must be sent into hospital, or should be assessed on the advice of a consultant. Thus, I can show that whereas there were 13 cases of eclampsia in 1951, 1952 and 1953 there has only been one case since 1954, and that in a non-booked case. In fact since 1951 there has only been one case of eclampsia in a booked case (postpartum, one fit). The average total deliveries each year in the Professorial Unit is 1,300, 80% of which are booked.

When the results after the use of hypotensive agents such as sodium amytal, Apresoline, phenobarbitone, Serpasil are assessed the fœtal death-rate is independent of effective lowering of the blood pressure. The relationship between the severity of the condition of toxæmia—particularly in the presence of albuminuria—and fœtal mortality is a close one. No less intimate is the association between the maturity and fœtal risk. In my opinion the results we have obtained do nothing to alter the view that placental damage once sustained is irreversible, and fœtal survival depends on the amount of residual functional placental tissue and the fœtal maturity.

Knowing then that even a mild toxæmic episode can lead to some degree of placental ischæmia (Browne and Veale, 1953) and appreciating the possibility of placental insufficiency in the post-mature (Walker, 1954), recently confirmed by MacKay (1957), even a cured mild pre-eclamptic should have labour induced at 38–39 weeks, or, should the toxæmia recur, at any rate after the 36th week. Indeed, MacKay has this to say: "the infant who is in a very dangerous situation is one whose mother has been suffering from a long-continued mild toxæmia and who is allowed to become post-mature. The cord oxygen levels in these cases may be truly desperately low." There should be no combination of post-maturity and even mild pre-eclampsia.

Changes of Method of Induction

I. *Methods:*

(1) *Medical induction:* Oxytocic drip.

(2) *Surgical induction:* (*a*) Rupture of forewaters. (*b*) Cæsarean section.

(3) *Combined medical and surgical induction:* (*a*) Rupture of forewaters followed by oxytocic drip. (*b*) Oxytocic drip followed by rupture of forewaters. (*c*) Cæsarean section after *a* or *b*.

(*a*) *Rupture of the Forewaters*

Since 1953 the Drew Smythe catheter has not been used. All surgical inductions, therefore, are now by rupture of the forewaters. This change was precipitated by a maternal death from sepsis (the only death from sepsis) after a Drew Smythe induction of labour for toxæmia. Three days after induction the patient died in the second stage of labour, and at post-mortem there was found a pool of pus between the membranes and the uterine wall, at the site of the puncture. Obviously, the cardinal principle of "where there is pus let it out" had not been obeyed. Since then, in 1954 and 1955 a series of 987 surgical inductions by rupture of the forewaters has been carried out. 51% of these inductions were for pre-eclamptic toxæmia and essential hypertension. Only 13 cases developed genital tract infection giving rise to notifiable pyrexia, and in this connexion I would lay stress upon adequate vaginal toilet as well as vulval toilet before vaginal examination prior to induction. In this series of inductions there were no maternal deaths, stillbirth rate (corrected for abnormalities) was 1·1% and the neonatal deaths (corrected) was 0·5%. The Cæsarean section rate was 1·94%. There were only two cases of prolapsed cord. From experience then I believe that rupture of the forewaters is the more reliable method of induction of labour, and it does not matter whether the head or breach is free or engaged. 78% of this series were delivered within forty-eight hours of induction, and only 3 cases had a prolonged first stage of labour following rupture of the membranes. 81% were delivered following a first stage of twelve hours or less. A comparable series with not such good results when using a Drew Smythe catheter has recently been published by Manly (1956).

(*b*) *Oxytocic Drip*

All cases of induction for toxæmia should have a vaginal examination to determine the state of the cervix. If the cervix permits rupture of the forewaters then this should be carried out. If the cervix does not admit penetration by the finger and the case is the more chronic variety of pre-eclampsia, then an oxytocic drip (Syntocinon) is set up in an attempt to open up the cervix. This drip, similar in every way to the one employed twenty-four hours *after* rupture of the forewaters, is started with 1 unit of Syntocinon in a bottle of 5% glucose solution (540 ml.). It is regulated at a rate of 12 drops per minute rising at half-hourly intervals to a total of 60 drops per minute. 5 units of Syntocinon are put in the second bottle, again starting at a rate of 12 drops per minute. When uterine contractions occur the drip is maintained at *that* same number of drops and is continued until labour has been completed. Formerly, the drip was not set up until forty-eight hours after rupture of the forewaters, but this has been advanced to twenty-four hours after rupture because of urgency in many cases of pre-eclampsia. If the drip is being used to open up the cervix it will take at least forty-eight hours, and maybe even slightly longer before the cervix is sufficiently dilated to permit forewater rupture. If the membranes have been ruptured for forty-eight hours and labour not completed chloramphenicol is given. This was the preparation decided in consultation with the pædiatricians and which we have used now for some four years. Recently, Smith *et al.* (1956) advocated streptomycin and oxytetracyline in such cases but we believe that adequate cover for baby and mother is provided by chloramphenicol without risk of blood disease and without painful injections.

Theobald *et al.* (1956) reviewed a large number of cases which had had oxytocic drips and they advocate a dilution of 1 in 10,000 and 1 in 5,000 with the drip maintained at a rate of 40 drops per minute. This drip is set up with supervision by the house surgeon only for the first half hour when fœtal distress may occur and the drip may have to be taken down. I tried Theobald's procedure but with less success than my own method as far as the onset of labour was concerned.

Since June, 1954, oxytocic drips have been used at Southmead Hospital in an average of 10% of cases. It is noticeable that if the drip percentage falls the Cæsarean section rate rises. Out of 81 oxytocic drips used in cases of toxæmia at Southmead Hospital there was only one fœtal death (32 weeks, blood pressure 210/130, albumin +++).

Pethidine is used as indicated during drip therapy.

(*c*) *Cæsarean Section*

I find that other indications for Cæsarean section occur in an average of 25% of toxæmic cases. Where toxæmia is the only consideration I would say that Cæsarean section has to be employed (1) for the acute, very premature case of pre-eclampsia and (2) in the more chronic case where the pre-eclamptic state is deteriorating and labour has still not ensued after surgical and (or) drip induction and (3) in a very few cases of eclampsia. In failed drip cases, and these are very few, it is wise to ponder that the activity of the female uterus is not always readily stimulated even after rupture of the membranes in cases of post-maturity, and Baird (1955) has shown the influence of age in this connexion. Whereas Cæsarean section was used more frequently in cases of toxæmia some years ago, it is only seldom used now when toxæmia is the only indication, and in this series for the past three years has been used in slightly over 3% of cases each year.

Cæsarean section in toxæmic accidental hæmorrhage is seldom indicated. The combination of anoxia and prematurity is highly dangerous for the fœtus, and the results obtained do not justify the use of Cæsarean section at any rate until near maturity.

Results

(1) The fœtal salvage rate in toxæmic cases from 36 weeks onwards in my series was (and should be) almost 100%. Before 36 weeks, including early cases, the fœtal salvage rate is just over 50%. (Stillbirths and neonatal deaths almost equal in number.)

(2) Comparing 1951 and 1956 figures of induced toxæmic cases there has been an overall improvement in fœtal salvage of 5%. This does not illustrate the whole picture, however, because now the improved results are obtained with greater ease and avoidance of worry by rupture of forewaters (61% of cases), oxytocic drip before or after rupture (10% of cases), and Cæsarean section is only just over 3%.

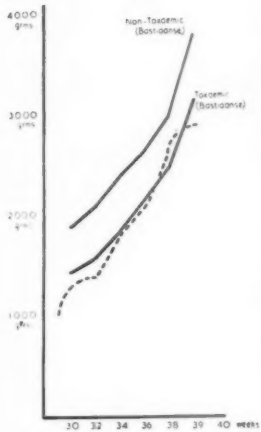


FIG. 1.

There remains a hard core of stillbirths and neonatal deaths in 6·5% of non-induced cases, almost the same figure for both years 1951 and 1956. They include intra-uterine deaths, not only in emergency cases, and it would appear that they result from a reluctance to induce labour in some cases, particularly when the degree of prematurity is great. A bolder approach in future may salvage some of these.

(3) Fig. 1 illustrates the mean size of baby at different stages of gestation in normal pregnancy and in toxæmic cases. The graph was compiled with the use of Bastiaanse's figures (1956), and also the mean weights of the stillbirths and neonatal deaths (presumably the more serious cases) in my series. Babies from toxæmic mothers weigh less on the average than do babies from normal mothers. At 32 weeks in the toxæmic case one can expect a baby of 3 lb., at 34 weeks one of 4 lb., at 37 weeks one of 5½ lb., and at term a baby of 6½ lb.

I have great pleasure in recording my thanks to Dr. T. E. Oppé, Dr. G. Herdan, Mr. S. R. Hewitt, Mr. E. M. Edwards, and Mrs. Doreen Hillier who helped prepare this review.

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Mr. C. Keith Vartan:

Plea for Standard Normal Blood Pressure

The recording of the blood pressure in the pregnant woman is so important a feature in hospital practice to-day that it seems hardly credible that as recently as twenty-five years ago, it was not a routine procedure at all. In 1940 the ante-natal case papers supplied to the midwives of a well-known County Council contained no column in which this observation could be noted. This is just one illustration of the state of affairs then pertaining. The blood pressure received attention when the presence of albumin in the urine was noted. The obstetrician, in short, has not been interested in hypertension for very long, which is probably the explanation that we are still not agreed among ourselves as to what we will accept as the upper limit of normal blood pressure, and why we have no common language when we come to discuss the vitally important subject of the hypertensive manifestations in pregnancy, a Gilbertian situation, in the words of Jack Point "What is all right for B would quite scandalize C (for C is so very particular)". Figures varying from 130/70, to 150/100 are held to be normal. The standing Maternity and Midwifery Advisory Committee of the General Health Services Council of the Ministry of Health suggests a diastolic pressure of over 90.

Bastiaanse (1956) has written "There is no consensus of opinion as to the maximum value above which the blood pressure must have risen to be defined as hypertension", and goes on to state "it would be very desirable to reach a unanimous opinion with regard to this

matter". Gibson in his papers of 1954 and 1956 on the "Prognosis of Toxæmia of Late Pregnancy" states that "there is no measure of agreement as to what level of blood pressure should be considered as evidence of chronic hypertension" and later "Comparison with the experience of others is of doubtful value because so much depends upon the level of blood pressure which is accepted as evidence of hypertension".

This independence of thought constitutes a great stumbling block when it is applied to the treatment of pregnant women, and we should by now be ready to accept one standard throughout the country. The general physician has of course been interested in the blood pressure for far longer than has the obstetrician, and reference to their standard works show that with remarkable unanimity, they postulate that 120/80 is the normal blood pressure. Yet how much more important is the dramatic and fitful progress of the blood pressure in pregnancy than the measured tread of this disorder in the non-pregnant state. We might well ask, "by what right does the individual obstetrician chose his own individual standards".

In 1933 F. J. Browne writing of the early signs of pre-eclampsia enunciated his view that we should all accept the 130/70 standard (since changed to 120/80). This pronouncement was kindly received but the general consensus of opinion was that this figure was impossibly low, that far too many normal women would thereby be classed as abnormal. This adverse reaction could not have been based on the experience of those who were criticising Browne; they had not till then thought in terms of 130/70, neither was it supported by the opinion of the general physicians. Browne's dictum has not been refuted subsequently by workers in hypertension. Many obstetricians still hold the view that 130/70 is unrealistic and some have gone further and have said that Browne has done a disservice to obstetrics by this pronouncement. One can only hope that this rejection is not based on the fear of having too many patients *needing treatment* on their hands.

Leo Hahn (1952) in an extensive study of adolescent schoolboys found a mean reading of 117/67 at the age of 15 and he quotes other workers who show what one might expect in examining a large number of young men. In a study of the blood pressure of 6,000 prisoners Alvarez and Stanley (1930) found as high an incidence of hypertension at the age of 15 as at the age of 40. Hines (1937) using the "cold test" as a means for detecting hypertensive cases among 400 school children, found 18% of hypertension. Robinson and Brucer (1939), reporting on 11,000 persons' blood pressure readings, stated that the normal range of systolic blood pressure for men and women is from 90 to 120 mm. of mercury and that the normal range of diastolic blood pressure for men and women is from 60 to 80 mm. of mercury. They stressed that a normal person reaches his mature blood pressure at about adolescence and keeps that range throughout life. In the light of these observations, we should expect to find from 15% to 20% of our patients to be hypertensive, but no more, even on the 130/70 standard.

I believe that the high incidence of eclampsia is very largely due to the regarding of figures well above 130/70, as being still within the normal range.

The prime purpose of this paper is to put on record the results recorded during the last eight years at a hospital where rightly or wrongly the 130/70 standard is adhered to, so that the extent of the problem, that is the number of patients who, in fact, must be regarded as abnormal, and who have to be admitted for ante-natal supervision, can be shown. Secondly, I shall compare the behaviour of patients commencing pregnancy with a normal pressure, with those who are hypertensive on booking, a study which has not previously been made. Throughout the paper the term pre-eclampsia will be used only for those patients whose blood pressure was below 130/70 on first booking (if in the first twenty weeks), and in whom the blood pressure subsequently rises, and the term hypertension for those who are already above this figure (either figure above, but neither below) on first booking.

The women booked at this hospital are primiparæ; multiparæ who have had some abnormality during the previous pregnancy, labour, or puerperium; women who have a general medical disease; and inevitably a number of women whose home conditions make hospital confinement desirable. The borough in which the hospital is situated has its prosperous parts but it also has its slums. There is, however, no economic selection. The hospital has 63 maternity beds and bookings are made on the basis of 20 patients per bed per annum. There are no beds designated for ante-natal care alone.

Hypertension

During the last eight years 10,682 women have been confined and of these 1,077 had a blood pressure of above 130/70 on booking. Thus 10% of all women primiparæ and multiparæ, young or old, who book are hypertensive, but what is surely more striking is that 90% are, in fact, below the Browne 130/70 standard.

The criterion for admission to hospital is the coincidence of albuminuria or of œdema or of excessive weight gain. All of which are associated with a further rise in B.P. 18·1% of these 1,077 developed albuminuria and 36·9% developed œdema. Thus about 40–50% of these hypertensives deteriorated and were admitted. This seems a high admission ra

for any hospital and particularly for one with no designated ante-natal beds but it must be related to the stage of pregnancy at which these women are admitted. In 1955 it appeared that of the 113 patients admitted, 25 were within two weeks of term and 52 were at or beyond term. In practice these 77 patients would be considered for induction either at once or after a few days' rest, because the pregnancy aggravates the hypertension. They therefore present no problem of prolonged ante-natal bed occupation.

If we deduct the patients at 38 weeks or over from the list of 113 we are left with only 32 who would require a period of bed rest of over a week. 14 others (36 and 37 weeks) might or might not have to wait, according to the size of the baby.

The most important treatment which they have is rest; possibly a low sodium diet if they are very œdematous, usually a mild sedative; hypotensive drugs have been tried but without much apparent success. Most patients respond to rest fairly quickly. Their blood pressure falls and the albuminuria does not increase. If there is no albumin in the urine a patient may be allowed to go home after a short period of bed rest. If, however, she is within a week or two of term, induction by rupture of the membranes is preferred. This is the logical treatment; it is the pregnancy which is exacerbating the hypertension; therefore, we terminate the pregnancy.

Unfortunately the figures for 1948 are incomplete, but in the following six years 245 patients or 28·7% of this group were induced on this account.

The antagonism to the practice of rupturing the membranes is probably weakening but that is not to say that it can be lightly undertaken. The operation must be performed with proper surgical skill if it to be successful.

Cæsarean section was performed on 18 occasions. There has been no maternal death in these 1,077 hypertensives. There were 23 stillbirths and 11 neonatal deaths in the eight years. All cases are included, there has been no "correction". The percentages are 2·13% and 1·2% respectively. No woman developed eclampsia.

Pre-eclampsia

The women whose blood pressures were below and stayed below 130/70 till the second half of pregnancy and then rose number 1,631, an average of 204 per annum. The stage of pregnancy at which they are admitted, and again about half of these require admission and for the same reasons, œdema, albuminuria and excessive weight gain, is given for the same year (1955) as in the hypertensions. The total admitted was 119.

In this group 36·7% develop albuminuria and 60·9% develop œdema. It should be noted that in the pre-eclamptic group 97 out of 119, or about 4/5 of the total may be induced forthwith and that 22/119 or 1/5 must have a period of rest in bed first, whereas in the hypertensive group who come under observation earlier, the number suitable for induction at once is smaller.

The treatment in hospital is basically the same but differs in this important criterion: no patient is allowed out undelivered. 652 women were induced in the eight years or 80% of all the pre-eclamptics admitted. There were also 24 Cæsarean sections performed.

The stillbirths numbered 53 (3·12%) and the neo-natal deaths 17 (1·04%). There was one maternal death from anuria in a women who developed post-partum eclampsia. There were altogether 4 women in this group who developed eclampsia; 4 in 10,682 or 1 in 2,670.

We are now in a position to compare the two groups (Table I).

TABLE I

	Hypertension	Pre-eclampsia
Incidence	10%	15·2%
Developing albuminuria	18·1%	36·7%
Developing œdema	36·9%	60·9%
Maternal death	0	1
Stillbirth	2·1%	3·12%
Neonatal death	1·2%	1·04%
Perinatal mortality	3·3%	4·16%
Subsequent developing eclampsia	0	4
Induced	28·7%	80%

(The total fœtal and neonatal loss is 3·73%)

This comparison has not been made before but I believe it shows one thing of great clinical importance, namely, that, in general, a hypertensive subject can take whatever this thing is that happens to her in pregnancy, better than the woman who was normo-tensive in the first half of her pregnancy, but who later deteriorates, although of course the very severe hypertensive (such as is not often seen in pregnancy) may be more likely to come to harm than a mild pre-eclamptic.

From these figures, too, it seems that her chance of developing eclampsia is less, but with only 4 cases in eight years it was necessary for me to turn further afield. I wrote to and received replies from Belfast Maternity, Bromley, Dartford, National Maternity Dublin,

Elsie Inglis, Glasgow Southern General, Guy's, Leeds, Liverpool, Manchester, Melbourne, Oxford, Newcastle-upon-Tyne, Queen Charlotte's, the Rotunda, St. Thomas', Southend, University College and Woking, and was thus able to collect information concerning 160 cases of eclampsia in booked patients. I asked just one question: what was the commencing blood pressure of the patients who developed eclampsia? Non-booked admissions are not included as this information was not available.

Summarizing the information received regarding the 160 cases of eclampsia it is found that 118 started their pregnancies with figures of or below 130/70 whereas only 42 started as hypertensives by this standard. Translating this into percentages we see that 73·4% of eclamptics start with a normal blood pressure and only 26·2% as hypertensives. Only 5% started pregnancy with a diastolic pressure of over 90. This is the second important point which emerges, and is of the greatest importance when it comes to treatment: one may take chances with a hypertensive but never with a pre-eclamptic.

Samuel Bard in his Compendium of Midwifery (Collins and Perkins, New York, 1808), stated that "if early attention would be paid to the signs and symptoms described they might not only be relieved, but the more dangerous state of convulsions which they threaten, would probably be prevented".

Hamlin states that eclampsia is a preventable disease. I agree, but one needs a little luck as well, for a woman may pass all the criteria of normality at her last attendance and delay for a day or two before seeking advice for her swollen hands and headache. The vital importance of "self-observation" must also be stressed to the patient, but all our watchfulness is jeopardized if we set a standard higher than the 130/70 originally advocated by Browne, and start our watching too late.

If further emphasis is necessary the published incidence of eclampsia at different centres in Britain should be compared with the 1 in 2,670 of the present eight-years series, and which should surely be attainable everywhere.

TABLE II.—INCIDENCE OF ECLAMPSIA AT DIFFERENT CENTRES IN BRITAIN

Hospital	5 years	Cases	Incidence
A	1946–1950	17 in 7,071	1 : 416
B	,,	19 in 8,743	1 : 460
C	,,	8 in 5,127	1 : 641
D	,,	21 in 13,501	1 : 643
E	,,	9 in 6,220	1 : 692
F	1949–1953	13 in 9,003	1 : 692
G	1946–1950	12 in 11,072	1 : 922
H	,,	4 in 3,937	1 : 984
I	,,	5 in 5,798	1 :1,159
Control	1948–1955	4 in 10,682	1 :2,670

These are the only hospitals from which consecutive maternity reports have been received: four are London teaching hospitals, three provincial teaching hospitals and two non-teaching hospitals. The standard B.P. at these hospitals is, in general, a diastolic of 90.

I think I have shown that eclampsia is most prevalent in those hospitals and schools where the information obtained by those who have studied the normal blood pressure has been so lightly set aside.

The occurrence of eclampsia is, of course, much higher than I have shown, for most of the eclamptic cases occur in the home and are admitted as emergencies, but we must remember that all practitioners and all midwives are, in the first instance, taught what they now regard as normal and abnormal.

The Minister of Health has shown that "the principal cause of avoidable maternal death in this country is toxæmia of pregnancy".

I believe the responsibility rests fairly and squarely on the shoulders of all who resist Browne's teaching. I believe we must radically change our complacent outlook and start teaching that 130/70 is the normal pressure for a pregnant woman.

CONCLUSIONS.—(1) Eclampsia is virtually a preventable disease. (2) It is not in the patients' best interest that obstetricians should disregard the advice of the physician that 120/80 is the normal blood pressure. (3) Comparisons of methods and results of treatment are impossible when variable standards are used. (4) Women who are hypertensive at the beginning of their pregnancy are a better risk than normal women who later develop pre-eclampsia. (5) A hospital which accepts the 130/70 standard must be prepared to admit 18·5% of its patients before they go into labour spontaneously, but of these over half are so near to term that they may be safely induced forthwith.

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Section of Psychiatry

President—WILLIAM SARGANT, M.A., F.R.C.P., D.P.M.

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The Brain as a Machine

By W. GREY WALTER, M.A., Sc.D.
Burden Neurological Institute, Stapleton, Bristol

THE title of this paper needs some explanation. Physiologists are accustomed to speaking of organs of the body with a definite article, assuming that all such organs are essentially similar, at least in a given species. Human brains may be an exception to this convenient rule, since, however we may choose to describe cerebral mechanisms, we must accept the evidence for personal variations, and these variations may be the main diagnostic character of highly evolved central nervous systems. In fact, psychiatrists and psychologists seem to imply something of this nature when they consider stereotypy as a sign of mental pathology. This is not to say that we cannot envisage *any* features common to all human brains but we should realize that whatever general picture we may form of the mechanics of brain function should include a high potentiality for individual idiosyncrasies.

The term "machine" also is liable to misinterpretation. We still tend to think of machines as though they were simple devices to amplify or conserve human muscles but a much wider definition is permissible and indeed essential if we are to consider more than the simplest aspects of mental behaviour.

The problems facing brain physiologists to-day are novel from the standpoint of classical biology, but they are not very unlike those familiar in other sciences. It is perhaps in meteorology that we find the closest resemblance to human neurophysiology, for in charting and predicting weather conditions a meteorologist must take into account the operation of a large number of interacting mechanisms, most of which are mysterious in their origin, though all are capable of exerting a major influence. There are serious and well-known risks incurred when prediction is based on empiricism, as anyone may quickly learn who plans a picnic in England in August, but many of these risks are due to the difficulty of distinguishing between large-scale and small-scale phenomena. Fine weather does not exclude the possibility of a local thunderstorm and, in fact, may even promote it. Similarly, in the physiology of the brain a high-grade normal level of function does not exclude the possibility of epileptic seizures; I have suggested elsewhere that the very refinement of normal discrimination in human brains may actually increase the possibility of convulsive breakdown (Walter, 1953).

The science of brain mechanics is at an awkward age of its development, relying still on classical terms but attempting to explore the frontier of evolution. We are in the pre-Newtonian age as it were, in which we can still argue amiably in terms of Cartesian vortices, though we may feel that at any moment a theory of Gravitation may destroy and simplify our web of fancy. If we find the associations of the word "machine" too instrumental, we should perhaps recall that the etymological meaning implies simply *a way of doing something;* we should be encouraged therefore to study behaviour rather than static structure even though we may still lack the tactical equipment for detailed analysis of complex systems.

The first question we should ask presumably is "What does the brain do?" A specific answer is not so easy to frame. One can say plausibly that the brain does everything we can think of, but this is of no great help in the design of an experiment nor presumably in the examination of a patient. If the question is differently phrased, the answer may be more explicit. Knowing from prior information that much bodily behaviour is implemented by interacting reflex circuits, we may legitimately enquire how complex a behaviour pattern can be formed by such a system of reflexive action. This enquiry yields immediate gain for we find ourselves transported into the new kingdom of cybernetics; the physiological reflex is an older and, I think, clearer term for what engineers call "servo" or "feedback systems".

The cybernetic approach to this domain is both practical and powerful. There is now a great mass of information on the nature and action of reflex systems in flesh and metal. The early notions of neurophysiologists are unconsciously embodied in many of them, but are extended in some to a degree which is hard to emulate in a physiological laboratory. Many of these intricate analyses can be demonstrated by the operation of working models, as has been shown by Ashby (1952), MacKay (1956), Shannon (1952), Uttley (1956), Wiener (1950) and myself. It can easily be seen, for example, that a system with only two reflexes can display an astonishing variety of apparently "purposeful" behaviour patterns.

Such a model can easily find its way around quite a complex world. It can avoid starvation or self-destruction, it can attain its sources of nourishment and refreshment, it displays a commendable moderation in its quest for gratification and avoidance of pain, it can solve without difficulty the dilemma of Buridan's ass, it behaves as if it could recognize itself as in a category different from all other structures and others of its own kind in a related category as well. We may conclude therefore that mere complexity of behaviour does not inevitably require more than an assembly of reflexive circuits—a spinal cord.

Careful observation of the antics of such models reveals that elaborate though the behaviour patterns may be—and they may be so bizarre as to deceive even a trained observer of animals—they display no modification by experience, and such modification we must put in a different class from mere complexity. Here again, study of model behaviour suggests that there is one class of adaptation still outside or below the domain of brain function; this is the type of improvement in performance by repetition which may be, and often is, achieved by a process no more sophisticated than the running in of a motor or the wearing out of a garment. Modification of this type is sometimes referred to as practice. The really interesting part of brain mechanics would seem to reside in the fine structure of that behaviour which we usually describe as thinking and learning. We may then consider specifically, how may human brains perform these functions? Again, study of working models of learning can assist us, for in their design the first article of the specification requires that they exert a power of selection over the information they receive. Like an ordinary radio set, a learning instrument is useless if its reception is too wide. It must be capable of tuning itself, as it were, to selected stations. The significance of a signal is not necessarily increased by multiplication of sources. We must therefore investigate the mechanism whereby a human brain can be tuned—or can tune itself—to those sources of information which it can identify as "wanted". As a first step in such a study, can we decide what the information is wanted for? We must suppose at least that, in general, it is wanted for the survival of both the individual and the species, but in either case the aim is essentially statistical or probabilistic. That is, the justification of an aim is not necessarily logical, though a logical goal may often be considered as a special case or part of a statistical situation.

This general notion, that the mechanics of brain function may be based on processes of statistical selection and reflexion, seems to me one of the most powerful of recent developments. It receives some support from the now familiar fact that logical reasoning, in the sense of syllogistic inference, is more easily and rapidly performed by standard computing machines than by human beings.

From the experimental standpoint, therefore, we are led to search for any part of the reflexive machinery likely to be connected with the powers of statistical selection and coordination which are suggested as essential in this hypothesis.

In many laboratories experiments are now in progress to study the details of learning in human beings with the modern aids of electro-encephalography and similar techniques. Although many claims have been made it still seems too early for evaluation of the results as a whole. There is some hope, however, of identifying certain features of a learning mechanism by specifications derived from theoretical analysis. Such considerations suggest that one of the most important aspects of such a mechanism would be a process analogous to that developed for automatic factories, whereby the flow of information and materials is coordinated in time so that the course of production is smooth and optimally related to the availability of components and the desirability of the finished article.

In a special sense, therefore, in the brain as in an automatic factory, time is of the essence. This does not mean merely that speed is of particular value, but rather that the sequence of events must somehow be preserved and classified. As a simple example, it is important for any creature to distinguish in some way between cause and effect, even in arbitrary terms. We must be able to decide for ourselves whether lightning causes thunder, or thunder lightning or whether both have a common cause. Even this simple problem is not as easy to solve as it might seem, bearing in mind the widely different rates of transmission of light and sound in the outside world and the even more intricately variable rates of propagation of nerve impulses arising from the eyes and the ears in the nervous system. Zeus and Electricity are names not explanations. We should recall also that in the elementary working models of reflexive behaviour, the provision of an autonomous scanning mechanism offered an immediate solution for many elementary paradoxes of choice and symmetry. One part of our experimental work has accordingly been directed to the detailed analysis of these brain activities which seem to maintain a regular though adaptable rhythm, in the expectation that these may be found to be related to the mechanism of process control required for the systematic evolution of adequate statistical behaviour.

Until recently the methods of analysis were inadequate to provide confirmation or refutation of these hypotheses but we now have available a method for displaying a

measuring with a new order of accuracy the time and space relations of electrical events in the brain. The methods used heretofore have depended in the main upon some form of integration, averaging or summation to achieve the necessary degree of resolution. For example, in the Wave Analyser introduced many years ago (Walter, 1943) the various frequencies present in an EEG record are separated out and the abundance of each component is then added up over a period of ten seconds so as to provide a spectrum of the brain activity over this relatively long period. Similarly in the Toposcopic Display System first described in 1951 (Walter and Shipton, 1951), the rhythmic variations in voltage were transformed into changes of brilliance of a scanning vector on a cluster of 22 cathode ray tubes which were photographed in such a way as to permit summation of regular components by superimposition on the photographic emulsion. More recently (Shipton, 1957) the toposcopic method has been extended and modified so as to provide a high degree of resolution with respect to time in each of the 22 channels. This has been accomplished by introducing a spiral scanning time-base upon which are projected the variations in brilliance corresponding to brain activity. The speed of this time-base can be very accurately controlled and adjusted, and since the scale is coiled helically on the tubes the length of the exposure can be considerably prolonged. This provides what is termed "line-to-line correlation".

In effect, the display consists of 23 concentric circles, each representing one complete rotation of the cathode ray spot, of which the brilliance is modulated by the incoming signal. If the rotation rate is, for example, one revolution per second, then the complete tube would be scanned in 23 seconds. At the other extreme, if the scanning rate is 23 r/s, then the time to complete the picture would be one second. The presentation is illustrated diagrammatically in Fig. 1.

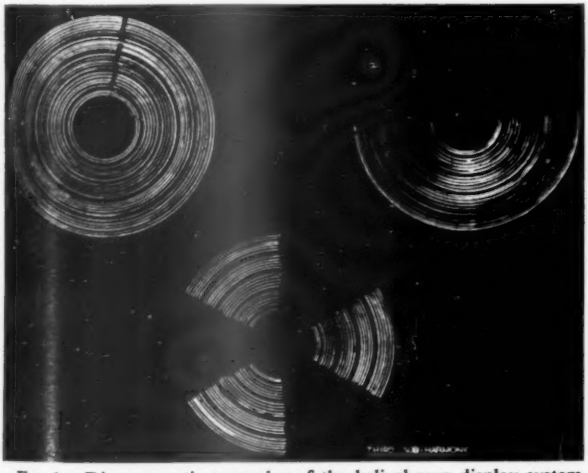
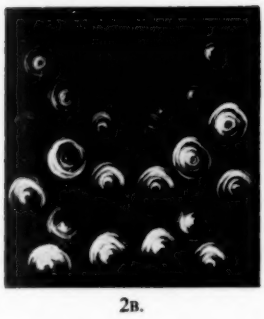


FIG. 1.—Diagrammatic examples of the helical-scan display system showing the 23 concentric circles. The gaps between the circles are to indicate time intervals during the exposure.



2A.



2B.

FIG. 2.—A, Alpha rhythms in normal subject at rest with eyes closed. The frequency varies from 8·3–9·6 c/s during the exposure but the phase relations in the various regions are consistent. B, Alpha rhythms in another normal subject with alpha frequency at 11·6 c/s again showing consistent phase relations which are similar to those in Fig. 2A although the frequency and distribution are different.

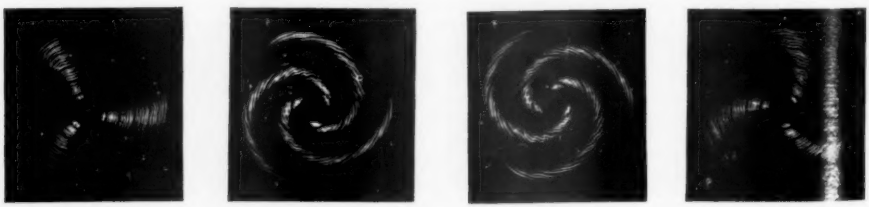
In this way records can be made either over a relatively long period with sacrifice of time resolution, or over a short period with a high degree of accuracy. For example, if it is desired to investigate the time relations of an alpha rhythm at 9 c/s the scanning rate can be set to nine revolutions per second and a device is available to lock the speed precisely to the frequency and phase of the incoming signal in one channel, which is then regarded as fiducial. Records obtained in this way are shown in Fig. 2, taken from two normal adult subjects. Here it is seen that the oscillatory waveforms of the alpha rhythms are represented as a group of black and white striped discs in the occipital region of the brain occupied by alpha activity; each line forming the disc is one "wave", and its length and brilliance indicate the wave

duration and amplitude respectively; in Fig. 2A the scanning frequency varied during exposure from 8·3 to 9·6 r/s. This was the range of variation in frequency of the alpha rhythm in the fiducial channel during this exposure, which lasted just under 2½ seconds. In each channel therefore there is a record of 23 waves and the time of occurrence of each wave in all channels can be seen at a glance, or, if desired, carefully measured. In this way can be obtained something approximating to an auto-correlation index for each channel and a cross-correlation index between channels. In this particular subject during this time it can be appreciated that this alpha rhythm is extremely regular in frequency and phase in each channel but the phase relations of the rhythm between channels are peculiar and intricate.

Fig. 2B shows a similar record taken from another subject whose principal alpha component was considerably higher in frequency—11·6 c/s. Here again there is a striking consistency in the time relations between channels. Furthermore, in spite of the difference in frequency and distribution of the alpha activity in the two subjects, there are marked resemblances in the phase relations between channels in both records. These records are two of a great many which exhibit unequivocal evidence that alpha rhythms do not occur precisely synchronously in all regions of the brain where they appear, but the time relations of their arrival may none the less be consistent over a period of several seconds, provided the mentality of the subject is undisturbed. These records were taken during rest, the subjects' eyes were closed and they had been asked to relax mentally as much as possible.

The next point to be established is that during the exercise of the mental faculties the consistent and coherent pattern of alpha distribution and time relations is elaborately but characteristically disturbed; this effect is exemplified in the next figure.

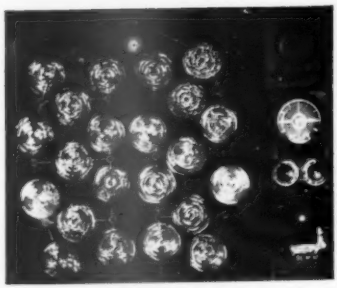
In order to follow the changes in alpha pattern associated with mental activity and stimulation, it has been found desirable to record at a scanning rate which is a sub-multiple of the rhythm to be investigated. This means that the exposure duration can be longer, while the estimation of time relations is correspondingly less accurate. When the scanning rate is exactly one-third of the frequency of the incoming rhythm, the records show patterns with three arms or petals which are perfectly straight, and, if the rhythm is entirely regular, with completely smooth edges. A test record of this type is shown in Fig. 3A. If, however, the frequency of the incoming signal is slightly greater than three times that of the scanning rate the three petals curl in a counter-clockwise direction (Fig. 3B). Contrariwise, if the signal is slightly less than three times the frequency of the scanning rate, the petals curl clockwise (Fig. 3C). The degree of curl—which can be seen at a glance—may be measured quite easily and indicates the precise frequency of the signal. In such an exposure the frequency of an alpha rhythm can be measured to an accuracy of 0·02 c/s (Fig. 3D). If measurements are made of each line, then it is possible to estimate the interval between individual waves as well as the over-all frequency. A record such as this displays just over seventy waves altogether, and if the activity is apparent in all channels, the total number of waves displayed in a single photograph is slightly over 1,500. The amount of information thus displayed is therefore very great and is certainly large enough to permit trustworthy computations of the significance of any changes that may be observed.



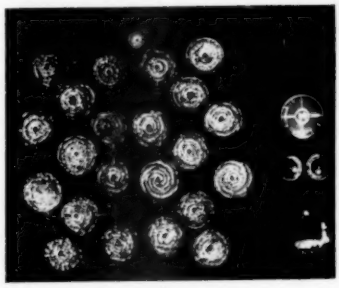
3A 3B 3C 3D

FIG. 3.—Test records showing the resolution of the display system run at one-third signal frequency. A, Signal at exactly three times scanning rate—9 c/s. B, Signal at 9·2 c/s. C, Signal at 8·8 c/s. D, Signal at 9·03 c/s.

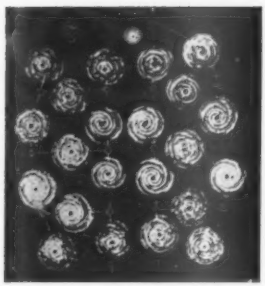
Using this method it has been possible to demonstrate clear changes in alpha frequency and distribution during moderate mental effort, and a series of such photographs is shown in Fig. 4. The first exposure (A), shows the alpha distribution and frequency at rest and corresponds with the high speed record in Fig. 2A. During the next exposure the subject was asked to perform a simple mental calculation; the immediate effect of the instructions was to suppress the alpha activity in all but two channels in the right hemisphere which were connected antero-posteriorly between the central, temporal and parietal electrodes. Even



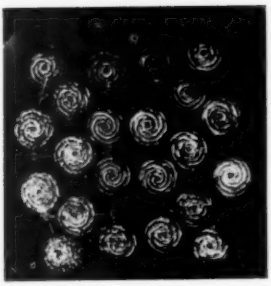
4A



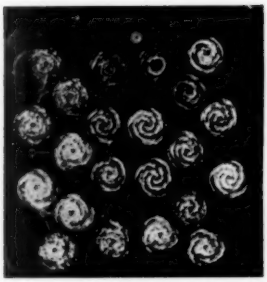
4B



4C



4D



4E



4F



4G



4H

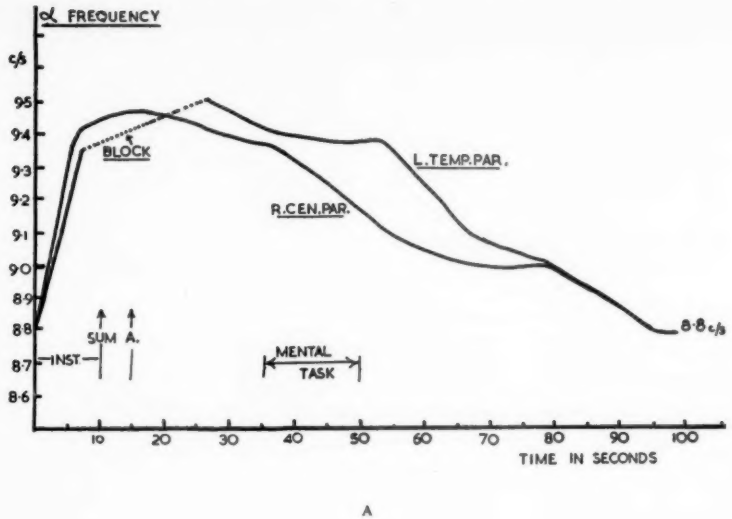
FIG. 4.—The effect of mental activity on alpha frequency and distribution in normal subject of Fig. 2A. The duration of each exposure was 8 seconds.

in these channels the rhythm was disturbed, as is shown by the curl of the three petals; the frequency in fact rose rapidly from 8·8 to 9·4 c/s.

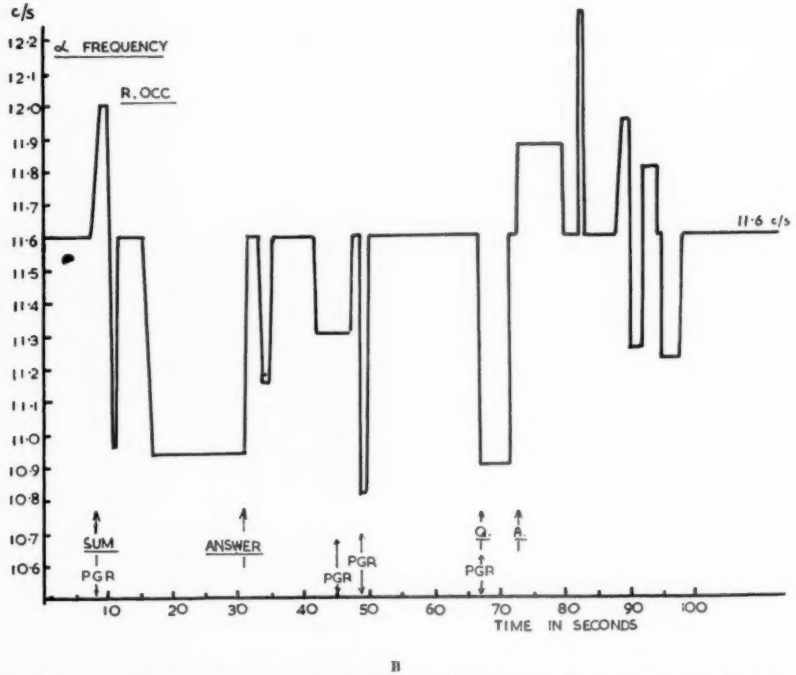
The other exposures in this series show a gradual return to the resting state. These are consecutive exposures, the whole set corresponding to a period of nearly two minutes. The solution to the first simple problem was given just before the third exposure, but the effect of the mental activity long outlasted the solution itself. The effect of the second task was much smaller and limited to the left side.

It can be seen that alpha activity gradually returned to the right hemisphere though at higher frequency than before, while the left hemisphere remained affected until nearly the end of the period of observation and on this side, even when activity returned, it was still of considerably higher frequency than on the right side.

In the last exposure but one, the right hemisphere has returned to its original frequency and distribution, but the petals in the left hemisphere are still curling, indicating a slight but significant discrepancy in frequency between the two sides. In the last exposure the original pattern is restored to an extraordinary degree of concordance.



A



B

FIG. 5.—A, Graph of changes in the alpha frequency derived from Fig. 4. Note sustained rise i frequency of about 0·5 c/s and final return to original frequency. B, Alpha frequency changes i normal subject of Fig. 2B and Fig. 6. Note abrupt frequency shifts and return to original frequency C, Alpha frequency changes in same subject as in A under the action of Meratran. The steady frequenc has risen by 0·4 c/s and the rate of change during attention is abrupt and discontinuous, but again th frequency returns to precisely its original value.

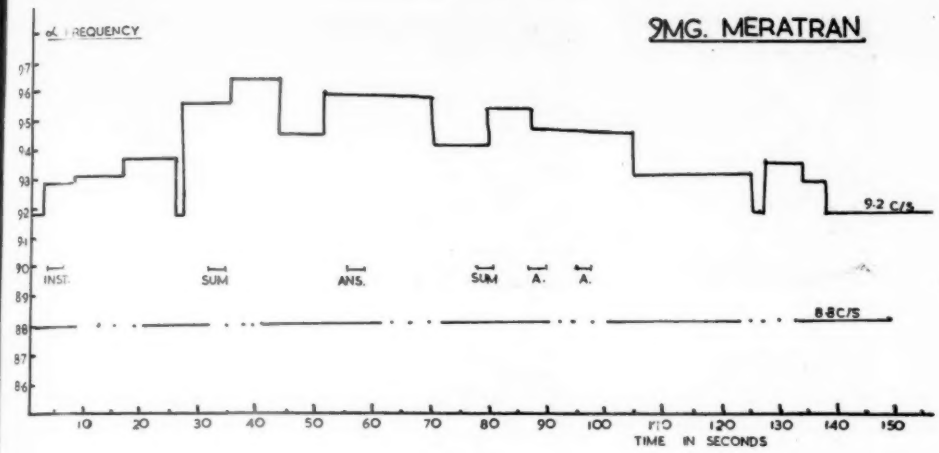


FIG. 5C.

In order to exhibit these changes in alpha frequency in a more conventional manner, a graph has been plotted (Fig. 5A) showing the rise and fall in frequency of the alpha component in the right centro-parietal channel during this very modest mental exertion and this is compared with the frequency change on the left side where, as already remarked, there was initially total suppression of rhythmic activity.

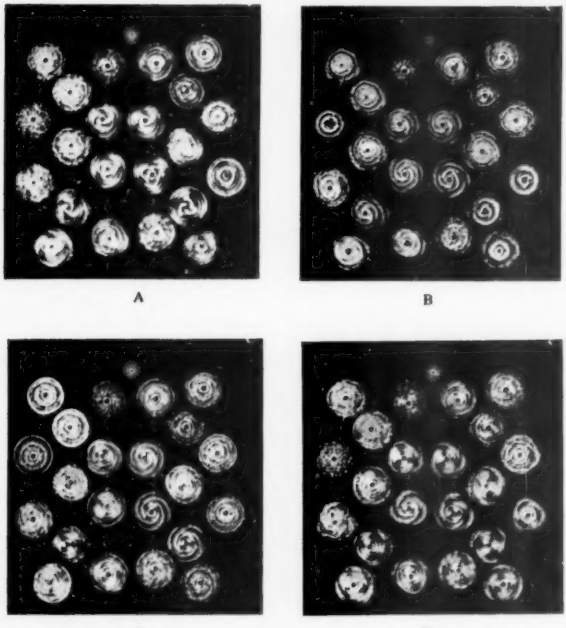
The most striking general inference is, that in spite of the pronounced and sustained alteration in frequency, the mechanism returned ultimately to precisely the same rate of discharge as before the experiment, even to an accuracy of one part in 100. It should perhaps be said again that a change of this order would be quite inappreciable in a primary record. It is just detectable with a wave analyser, but the interpretation of such variations in spectral distribution is inevitably ambiguous.

This set of records demonstrates that, as for example in the third exposure, a single quite restricted region of the brain can remain rhythmically active when all the rest is desynchronized. As a corollary, the two hemispheres, and even adjacent regions, may display complete autonomy of frequency and responsiveness.

There can therefore be no question of a supreme central pacemaker as has been suggested from time to time to account for the approximate synchrony and symmetry of spontaneous brain rhythms; nevertheless the degree of coherence and inter-channel correlation during rest suggests there is at times an appreciable tendency for some degree of synchrony. This tendency has been found to be a highly personal character and it may well be more important in relation to mentality than measurement of average or gross frequencies, since the way in which local rhythms fall into and out of step seems to be strictly related to the dynamic aspects of mental effort.

From the standpoint of mentality, consideration of these subtle changes in alpha pattern permits detailed study of the duration and extent of various types of attention and arousal. In the subject of the foregoing illustrations simple arithmetic problems provoked an effect lasting nearly two minutes, far longer than the time taken for the solving of the problem or the appearance of any overt action.

In the other subject, a normal adult woman, similar studies yielded quite different results. This subject has resting alpha rhythms with a mean frequency of 11·6 c/s in the occipital regions as shown in Fig. 2B. Fig. 6 shows the effect of mental activity in this subject. There is first a clear *slowing* of the activity in nearly all regions, then a return to the original frequency on the left side, then a further deceleration only in the left central region. Here again the pattern of response is absolutely typical of this subject in such conditions. A curve of the alpha changes in the right occipital region is shown in Fig. 5B. The whole character of the curve is clearly different from that of the first subject; there are abrupt shifts of frequency in both directions, mainly downward during periods of mental concentration. Most of these latter changes were associated with reduction of palmar skin resistance—psycho-galvanic reflexes. These records show particularly clearly the separation of the various alpha components in terms of both frequency and distribution. In other experiments, when this subject was threatened with punishment for failure to solve problems, the alpha frequency



A B C D

FIG. 6.—The effect of mental activity on alpha frequency and distribution in normal subject of Fig. 2B. A, shows the conditions during rest. B, Immediate slowing in all regions during the period of instruction. C, Desynchronization of the two hemispheres particularly in the parietal region. D, Desynchronization of the anterior and posterior regions in both hemispheres.

often *rose*, suggesting that the direction of alpha response may be a function of incentive quality.

For what it is worth—which may be little—these two subjects are very different in character. The first, who showed a sustained rise in alpha frequency, is original, speculative and persevering; the second, who displayed abrupt drops in frequency, is more receptive, conventional and erratic in her way of thinking.

As well as minute fluctuations in alpha frequency, other changes can be seen in these records. For example, in the subject of Fig. 4 an entirely new feature arose towards the end of the period of mental activity. The right frontal channel shows a component at about 3 c/s in the form of a single slow curl to the right in Fig. 4C and E; later, this component accelerated slightly (Fig. 4F) and then settled down to exactly 3 c/s (Fig. 4G). This was seen only during a period of mental activity and seemed to be associated with the return of the alpha rhythms to their resting state. It is tempting to consider this feature as an example of a restorative mechanism operating to maintain mental homeostasis.

The question naturally arises whether the fine structure of alpha responsiveness as illustrated in these cases is a permanent, unalterable feature of the electrical personality. In normal circumstances this seems to be the case. Even the most trivial details of the alpha patterns displayed by this means remain constant over a very narrow range in the same subject. None the less, by the action of certain drugs these characteristic features may be transformed or contorted. For example, the male subject of Fig. 4 was unobtrusively given a dose of 9 mg. of the drug *Meratran*, well known as an activating agent. The effect of this is shown in the graph in Fig. 5C where the changes in the alpha frequency in the right occipital region are plotted on the same scale as in Fig. 5A. These observations were made an hour after the unconscious ingestion of the drug; neither the subject nor his close associates were ever aware that he had taken it, possibly because he was very tired at the time. The effect on the alpha rhythms is clear and unequivocal as shown in the graph. There was a fairly rapid and sustained rise in mean frequency from 8·8 to just under 9·2 c/s and furthermore when requests were made to perform mental tasks as in the previous examination, the frequency changed abruptly and returned from time to time to its new resting level. The peak frequency was not greatly above that recorded during the normal period, 9·65 as compared with 9·45, but the general pattern of responsiveness was more irregular with sharp steps superimposed upon a sustained rise. It should be remarked that an alteration of this type would be only just perceptible as a long-term effect with a wave analyser, and the abrupt fluctuations in frequency would be quite undetectable even with this aid.

As another example of the action of drugs, the subject of Fig. 6 volunteered to take 100 micrograms of the hallucinatory drug LSD 25. During the action of the drug she reported vivid visual hallucinations for about four hours, but her personality remained unclouded and unperturbed, with only a minor persistent depression. In this case the effect of the drug, as reported by others, was again to raise the average frequency of alpha rhythms from a mea

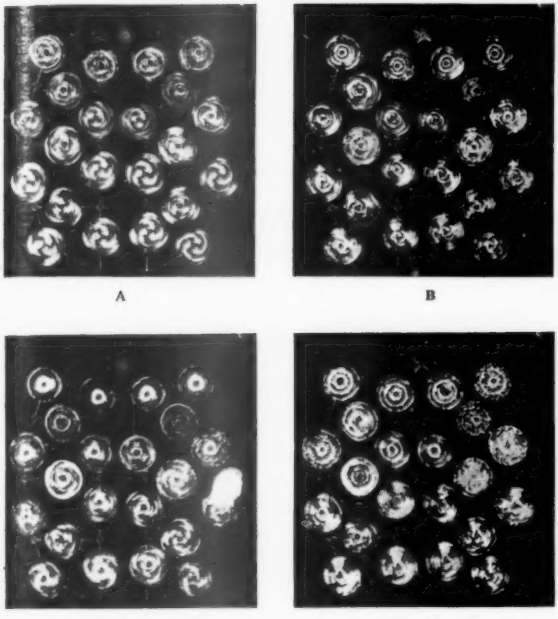


FIG. 7.—The effect on alpha frequency distribution of 100 gamma of LSD 25 in the normal subject of Fig. 6. A, Normal conditions before ingestion of drug. B, Comparison of normal alpha rhythms and flicker response. C, Acceleration of alpha frequency from 11·6–12·7 c/s and desynchronization of adjacent regions in the left hemisphere. D, Flicker responses evoked during action of drug.

of 11·6 to 12·7, which is considerably higher than the top frequency reached momentarily during mental activity in the normal state. Apart from this clear change in average frequency, there is a very marked alteration in the distribution and concordance of the various activities. In the normal state illustrated in Fig. 7A, the 11·6 c/s rhythm is everywhere synchronous and, in fact, the details of the various patterns are remarkably similar, even as far as the anterior frontal regions. Under the action of the LSD, however, the precise frequencies are quite different even in adjacent regions (Fig. 7C). For example, in the left occipital derivations, the parieto-occipital channel shows a clockwise curl indicating that the frequency is about 12·5 c/s whereas the near-by temporo-occipital channel shows a counter-clockwise curl indicating a frequency of about 12·8 c/s. This effect was observed during the greater part of the period of drug action and seemed to coincide with the phase of maximum hallucination. It does not seem unreasonable to suppose that this degree of disintegration in a subject whose alpha rhythms are normally closely synchronized may reflect a state of mind in which exogenous and endogenous stimuli are unusually dissociated. In Fig. 7B and D are examples of the effect of LSD 25 on the responses evoked by pattern flicker in the same subject.

These brief sketches from a physiologist's notebook are not intended to suggest that we are approaching anything like comprehension of the mechanics of mentality—they are merely illustrations of the evidence already to hand that there exist in the brain mechanisms which have that degree of order and consistency which we habitually associate with machines.

Earlier on, I pointed out the importance of "timing" in a mechanism such as we postulate in the brain. The extreme regularity and stability of the alpha processes in the subjects we have studied—and their subtle variations during thinking—suggest that there is here available a mechanism for preserving and comparing the sequence of events in time. Our present work is directed to investigating how these mechanisms operate during the course of learning and forgetting in human subjects. Such a study is unavoidably lengthy and elaborate, but there is already reason to hope that within a few years we shall be able to formulate a more detailed specification of brains as machines.

The observations reported here are the outcome of technical research and development by my colleagues, Mr. Harold Shipton and Dr. Raymond Cooper. It is a pleasure to acknowledge my gratitude to them and also to my friends who have acted as very patient subjects in these experiments.

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Dr. W. Ross Ashby: Until a few years ago we all thought we knew what we meant by a "machine"; our experiences with the alarm-clock and the typewriter seemed to provide an adequate basis for considering what a machine could or could not do. As a result, we tended to expect that no machine could do the complex and subtle things that the brain does. Whenever some mechanism was produced that did something brain-like we were surprised.

Those days are gone. To-day it is known that if any action or form of behaviour can be unambiguously specified, then there is undoubtedly a mechanism that can do it. For to-day there exists a well-defined routine by which the specification of the behaviour can be re-coded into the specification of a machine that will produce it.

To illustrate this fact, and to make the statement a little more convincing, I have here (Dr. Ashby demonstrated the machine to the meeting) a simple machine that can be so used to provide any demanded behaviour, provided that the behaviour is objectively defined and that it does not exceed the machine's capacity in size. I have chosen three forms of behaviour for demonstration. The machine is controlled by switches, which form its "input", and displays its behaviour on a row of lamps, which light and go out.

The first behaviour is simply the pupillary reflex. When a switch is closed (to represent "light shining into the eye"), the lamps light in succession from left to right, representing the movement of one edge of the iris towards the centre. When the switch is opened, the lamps unlight in reverse order. In this example the "contraction" is sustained as long as the switch is closed.

A second demonstration (after change of some linkages) shows the same reflex when the contraction is not sustained. Closure of the switch results in the lamps lighting across from left to right as before, but the lighting is not sustained, and one by one the lamps go back, from right to left, into the unlit state even though the switch is kept closed. Keeping the switch closed gives no further action. If, however, the switch is opened (representing "light no longer shining into the eye") and then re-closed, the "reflex" will appear again, but again fail to be sustained.

A third demonstration showed a behaviour with "memory". Before the switch is closed, nothing happens on the lamps. When the switch is closed, again nothing happens. The switch can then be opened again (i.e. the "stimulus" removed) and still nothing happens; but later, after a definite period of delay, the lamps light and show a characteristic (arbitrary) piece of behaviour.

These demonstrations *prove* nothing, but they illustrate the fact that the modern logic of mechanism (Ashby, 1956) is able to handle questions of the relation between structure and function with a completeness impossible ten years ago.

REFERENCE

ASHBY, W. R. (1956) An Introduction to Cybernetics. London.

Dr. D. M. MacKay: I should like to make a general remark on the limited usefulness of conventional quantitative mathematics in the theory of the nervous system, for I feel that Dr. Grey Walter may have been unduly apologetic in disclaiming an understanding of it. There are of course quantitative questions, concerning the information-capacity of a synaptic link or of a receptor organ, for example, to which one seeks numerical as well as qualitative answers. But I believe that the bulk of questions of psychiatric interest are organizational ones, demanding precise expression not in numerical terms but in the qualitative language of information-system theory.

The importance of this language lies, I think, in its ability to serve as a link between psychological concepts on the one hand and physiological concepts on the other. Hypotheses framed in terms of information-flow can, in principle, have implications—and so be tested—at both the psychological and the physiological level. With the development of even a skeleton "information-flow-map" of the nervous system, data expressed in the one language could begin to suggest hypotheses in the other (MacKay, 1954), so increasing the efficiency of diagnostic tests, and by the same token refining progressively the flow-map itself. What I am suggesting is quite different from the construction of a working model; for to those who understand a theoretical map a model shows little, while to those who do not, it often seems to show more than it should.

My point is that for the understanding of the general principles of such "maps" no high-powered mathematical training is required. The concepts involved (information-flow, control, selection, suppression, and the like) are more akin to those of administrative organization than to those of algebra. Inevitably, the "higher reaches" of this discipline, like any other, have their sophisticated techniques, and there is no royal road to their mastery. But I think it important to disclaim, as a theorist, any suggestion that psychiatrists lacking conventional mathematical training must find the theory of brain organization inscrutable, and must look to demonstrations by electronic "black boxes" as a less inscrutable substitute for understanding.

REFERENCE

MACKAY, D. M. (1954) *Advanc. Sci., Lond.*, **10**, 402.

Dr. F. H. George: The importance of the models which have been discussed lies largely in their value as research tools. They are more useful to some than to others; I myself think there is a great deal to be said for the use of mathematical models. Certainly they would easily include the sort of models so far built in hardware. I emphasize this only to try and avoid any false impression at a time when mathematical biology is rapidly coming of age.

I would also like to emphasize that I believe that discussions on whether or not machines can be made to think are liable to prove fruitless.

Section of General Practice

President—JOHN H. HUNT, M.A., D.M.

[*March* 20, 1957]

DISCUSSION ON COMMON CONGENITAL ABNORMALITIES AND THEIR MANAGEMENT IN GENERAL PRACTICE

Dr. Lindsey W. Batten: It is unlikely, but not inconceivable, that in England, even in London, and in 1957, a family doctor might conduct a confinement. Imagine yourself present at such an event.

Suppose the young mother has disdained anything stronger than pethidine, has endured the first stage, played her full part in the second and is now expelling her baby.

Out comes the head; the babe screws and unscrews its face, opens its mouth, utters its birth-cry and turns pink. Shoulders and body follow; the crying and the pinkness continue and four limbs move vigorously. What may now happen is this: our doctor clamps, ties and cuts the cord, glances at the genitalia, picks up the child and holds the little thing—vernix, caput and all—before its mother's delighted eye. "There, madam," he says, "you've got a fine boy."

The triumphant mother's womb contracts and expels the placenta. No post-partum hæmorrhage for her. Something provocative of lactation may happen in her breasts. In any case she "remembereth no more the anguish" but goes to sleep happy, confident and ready to repeat her admirable performance at some not too distant date.

Every instinct in me applauds the doctor's action—simple, direct, unevasive, humane and in tune with the physiological conception of childbirth and with our growing understanding of the psyche-soma partnership. And yet, in its implications, how careless of truth and how supremely imprudent! "Here, madam," the prudent and truthful doctor would say, "is the principal product of your conception. His genitalia are those of a boy; his heart and lungs are efficient enough to oxygenate his blood and to supply air-pressure for crying and his neuromuscular system is good enough for making faces, shouting and moving limbs. He does not look like a cretin, mongol or microcephalic but I cannot, at present, tell you whether he will ever see, hear, or display normal intelligence, whether his cardiac septum is complete, his aorta of normal calibre, and his ductus arteriosus closed or closing; whether his many tubes or ducts are pervious and properly connected; whether the femoral heads are in their cups or even, now I come to think of it, whether he has webbed toes or a gap in his palate. In fact he carries no guarantee of sound materials or good workmanship. Whatever his defects, they are no fault of mine so, if you are prepared to accept delivery on these terms, will you be good enough to sign this form of disclaimer?"

But there are limits, I think, to prudence and veracity no less than to light-hearted shutting of eyes. Like good Englishmen we shall compromise. "Here is your baby, madam, very much alive and looking fine, but I haven't examined him yet in detail and there may be imperfections. Have some tea and go to sleep. I'll tell you all about him when you wake up."

A mother who is worthy to be shown her just-delivered offspring should accept this easily enough and we must then turn to a purposive and well-directed examination to discover or exclude whatever abnormalities can be discovered or excluded at this stage.

Should he find any congenital defects how is he as a General Practitioner to manage these? Management presumably includes whatever prophylactic measures may be open to us.

I would suggest that there are three ætiological classes: the Bad Seed, the Damaged Embryo and the Pressure Group, with radioactive particles as a possible *causa causans* in classes one and two. In a free community and with our limited knowledge we cannot as a rule do much about bad seed, though it does fall to us as family doctors to stand between our younger patients and needless exposure to X-rays. At a recent post-graduate lecture

there was mention of a young woman who at 28 had had 23 X-ray investigations, chiefly, I think, abdominal, Such a patient's family doctor is surely the man to protect her, thinking, if no one else does, of the children she may hope to bear. Apart from this, we should be aware of the broad facts concerning familial disease and inherited defects and should be ready to advise.

Much more can be done to protect the embryo threatened by two malign influences—X-rays and rubella. A beautifully illustrated article in a clinical journal lists 13 "indications for inviting radiological examination" in pregnancy. They include verification of pregnancy at the 10th or 12th week, estimation of the placental site, and of fœtal maturity and, of course, pelvimetry so that, simply in order to "make sure", a healthy mother and her embryo and fœtus might be subjected to several considerable doses of X-ray in a single normal pregnancy. Strangest of all, a history of previous abnormal fœtuses is held to invite radiological examination. The writer mentions and discounts any risk of inducing cancer or leukæmia in the fœtus but makes no mention of the mother's future children or grandchildren or of the development of the embryo. If such investigations were proposed for a patient of mine without very weighty cause I should fall badly short if I failed to mention risks and counsel caution.

Rubella, to quote Alexander Joe, is an illness "with but little morbidity and no mortality" said to confer a solid and lasting immunity—in fact an innocent disease of childhood; yet a deadly foe of the developing embryo, responsible for some of the most horrible congenital defects—involving cochlea, labyrinth, eye, heart and brain—and almost certain to leave its mark if contracted by the mother in the first two months of pregnancy. "Many children," to quote Joe again, "escape the disease which is commonly contracted in adult life from the second to the fourth decade".

Knowing all this, how can we look on with equanimity while parents and at least some schools, impose quarantine for rubella on young children? Must we not put it diligently about that every female child should be set in the way of rubella at every opportunity until she gets it? A campaign by the public health authorities to this effect seems to be overdue, and the family doctor should raise his voice. Research might then provide us with the means to give rubella to every small girl in our practices, or to provide an anti-rubella vaccine or female children.

If a wife of child-bearing age, not immune to rubella, is exposed to it I think we must warn her of the risks of conceiving, giving her all the contraceptive help she may need, and if there seems the slightest risk of actual pregnancy, administer the necessary dose of gamma globulin. If she is not pregnant we should invite her to acquire the immunity while she has the chance.

Confronted by actual rubella in early pregnancy we cannot remain silent. We must declare the risks, perhaps first to the husband but probably best to husband and wife together. We should be ready with our facts. Broadly, the truth seems to be that in the first two months the danger to the baby, both qualitative and quantitative, is very great. The cochlea may still be injured in the third month. So great is the reported risk in at least the first two months that the question of terminating the pregnancy must inevitably arise. Carruthers, quoted by Banks in Garrod *et al.* (1953) states that "after the third month the probability of congenital malformations becomes remote" and we must not forget to say so. Perhaps we should not be too certain that the rubella virus is the only one that can play this fiendish trick. We should at least not erect barriers between the young child and mumps.

Some prophylaxis, then, is possible for the "Bad Seeds" and "Damaged Embryos"; can anything comparable be done for the "Pressure Group"?

Of the existence of this group there is no question. The general idea is not new. You may remember than when Mirabell, in "The Way of the World", puts up counter-conditions to those under which Millament is prepared to "dwindle into a wife" he says: "*Item*, when you shall be breeding—which may be presumed with a blessing on our endeavour—I denounce against all strait lacing, squeezing for a shape, till you would mould my boy's head like a sugar-loaf; and instead of a man-child, make me father to a crooked-billet." We need no Mirabell now. External pressure, if it ever was a factor, is gone long ago but the group is with us still. Eden (1906) said "moving freely in his bath of liquor amnii the fœtus thus takes exercise". What goes wrong in these cases? Clearly some disproportion between bath and occupant, but "oligohydramnios" is an unsatisfying explanation. Is the volume of the bath determined by the tone of its walls or by the volume or pressure of the water? Is there a natural device for adapting the bath's capacity to its occupant's size? Or is the little thing a sluggard, who lies there just growing until he finds himself woebound? Are the answers known? Must we remain quite impotent? Are physiotherapy, maternal diet, fœtal manipulation or stimulation or perhaps injection of hypertonic saline into the bath all quite useless? Here, surely, is at least a field for research, and possibly one for ante-natal measures in the home.

Our duty is to detect and identify the abnormalities as early and as precisely as we can and then take the right action which, when they are "palpable and visible", will generally be to know the right man for the job, consult with him and guide patient and parents in the right way.

Our responsibility—and, with it, our anxiety—will be greater with the invisible, impalpable defects, of which deafness and mental defect are outstanding examples. Blindness and "congenital heart" fall into the same category.

Except, perhaps, for mental defect, such vast advances in treatment, direct or compensatory, have been made in recent years that it has become correspondingly more important to find the defects early, to declare them when found and—what is peculiarly the family doctor's job—to make sure that everyone concerned does the utmost possible for the afflicted child.

Congenital deafness is a striking example of a condition in which mother and family doctor should work out the diagnosis together, in which, if they do this early, they can take the first vital steps in treatment and in the management of which they should continue in partnership for years. Expert help, if obtainable, will be of very great value but much can be accomplished without it. Special diagnostic apparatus is not essential and there is no place for surgery or medicaments.

We have two vital tasks: to detect the deafness early—in babyhood rather than infancy, and to enlist the mother's all-important aid. No neo-natal examination can reveal congenital deafness. There are no physical signs, and whereas the appearance and movements of a baby's eyes give news of their functional ability long before he can say "I see", his ears give nothing away.

Everyone watches the eyes for evidences of sight; it is useless to watch the ears for evidences of hearing; this is, therefore, apt to be taken for granted. We should not forget it, or mistake response to sight, vibration or movement of air for response to sound. Often enough deafness is not even suspected until the infant fails to speak, perhaps not even then. "Backwardness" is apt to be thought of first.

The sign that a baby *sees*—in the full sense of the word—is that he looks at and shows recognition or appreciation of the target of his looking; the sign of *hearing* is that he turns towards and reacts to a significant sound whose source he cannot see. Testing-sounds should be soft—a quiet, familiar voice, a food-preparing sound—the tap of a spoon against cup or feeding bottle—and in our general examination of a four or six months baby we should test the hearing in this way, as we test the sight with a toy, torch, handkerchief or familiar face. A single, unmistakable response is proof of hearing but if there is none we must be patient and test further with bell, drum, rattle, pitch-pipe, mouth organ or whatever we have, not forgetting that a sensible babe will see no point in vain repetitions but will get bored and disregard our pranks. We must have patience and continue when he feels fresh again, until we can form a reasonable estimate of his hearing. If he is indeed deaf then it is our special province to persuade his parents to accept whatever is proven fact—but no more. All is not lost, neither has this babe sinned nor his parents—it is no one's fault, and we can tell them with confidence that almost certainly some hearing is present, because it almost always *is*, though none may be immediately detectable. They must have faith and act on it, not by collecting a dozen "independent opinions" or by looking for surgical, medicinal, electrical or manipulative *cures* but by seeking and obtaining expert auditory training as soon as it can be had and above all by talking to the babe. They must talk distinctly, repetitively and often, casting the bread of words and phrases on the waters to find it in the child's speech after many days. There is, I understand, no substitute for the mother's voice, speaking into the ear at the acceptable time, which ends at 3 years old.

Wonders are done in cultivating and expanding the islands of hearing many of these children possess. In modern auditory training centres the deaf are taught to *hear*.

I have dwelt on deafness not from any special knowledge but because it illustrates so well the tasks that fall to the family doctor when any congenital defect, especially one not medically or surgically curable, falls from the sky into a family under his care. It is a taxing but rewarding task and it is our own.

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Dr. G. B. Mitchell-Heggs: It is difficult to know where "common" ends and "uncommon" begins when discussing abnormalities. "Uncommon" in general practice may mean fairly common in certain hospital skin departments, although rare in others. I noted a considerable difference in the incidence of certain disorders when working at the Royal

Berkshire Hospital, Reading, typical of a county town and country practice, as compared with St. Mary's and St. John's Hospitals, in London. Ringworm of the scalp and body, for instance, was more common at the former. Indeed, as far as the skin is concerned, there are no common congenital abnormalities apart from the nævus or, more strictly speaking, birth-mark group, with maybe ichthyosis thrown in for good measure.

Congenital disorders of the skin thus include the following: All types of nævi, that is to say, those which are abnormalities of the blood supply, which include nævus araneus, port-wine stain and the strawberry nævus; nævi in which the pigment cells are involved, that is, pigmented moles and melanomata and also junction nævi; those in which the epidermis is involved, or a combination of epidermis and dermis, in the verrucose or linear nævus. Urticaria pigmentosa may be described as nævus with mast cells in the corium and pigment cells in the basal layer of the epithelium.

Next are abnormalities of the epidermis; these are to be found essentially in babies in whom the sweat or sebaceous glands are not working adequately; it is rare to find a newborn child whose skin is working to excess with over-production of sweat or grease. On the other hand, an abnormal degree of dryness of the skin is not uncommon. In extreme cases, this can result in the condition known as ichthyosis fœtalis gravior.

In this group, therefore, there are all degrees from simple dryness or xeroderma to a marked scaling and bran-like appearance or ichthyosis (Fig. 1). Over-activity of the epithelium



FIG. 1.—Ichthyosis.



FIG. 2.—Vascular nævus.

round the hair follicles may lead to keratosis pilaris, and finally excessive production of horny tissue in the palms and soles results in keratosis palmaris et plantaris or congenital tylosis. A severe exfoliative disorder which occasionally occurs in nursing children is erythroderma desquamativum. It may be accompanied by constitutional symptoms and is generally fatal.

The next group of congenital abnormalities includes those in which there is a late or abnormal development of hair or nails, for which there is usually little one can do. Examples of these fortunately uncommon disorders include: monilethrix where the hair is sparse and brittle, with associated poor nail development, pachyonychia congenita, and congenital ectodermal defect.

Acquired infections that are of any significance are minimal, but it is important to mention congenital syphilis. As far as my department and private practice are concerned syphilitic babies have, practically speaking, disappeared, thanks no doubt to the excellent work done in general practice or in the Welfare, Maternity and other clinics.

So far as vascular nævi are concerned, there is considerable proof that the ordinary strawberry nævus tends to disappear with age, as we see so very few in children over the age of 5 or 6. On the other hand, those we do see give rise to considerable alarm among parents and relatives. Reassurance by the general practitioner or dermatologist is often not so convincing to them as a story that some baby had a nævus which started to bleed, and that no one could stop the bleeding.

In addition, babies are often brought because these vascular nævi are growing very rapidly. The mother has noticed that that particular part of the baby's body is unusually hot, and when the doctor sees it, he notices that a further growth of the lesion may cause other trouble. In other words, one round the mouth may interfere with suckling (Fig. 2), near the anus or vulva with defæcation or micturition, or near the eye, with vision.

In all such cases, if there is any doubt at all, it is important for the child to be seen by a specialist as soon as possible, and he is likely to recommend one of the following courses: (1) Further observation and no action. (2) Reference to a surgeon, for excision. (3) Reference to a radiotherapist. (4) The use of certain well-established procedures: (*a*) Injection

of sclerosing agents is often effective and fairly safe. (*b*) The carbon-dioxide snow stick, though first introduced over fifty years ago, can still produce satisfactory results.

It is important, however, that before these procedures are used, the surgeon or radiotherapist should be consulted, lest he feels that such preliminary treatment diminishes the ultimate chance of 100% success for his treatment.

So far as small fibro-cellular or pigmented moles are concerned, usually no action is required, unless they are more than a millimetre in diameter, or in a conspicuous situation likely to affect the child's beauty, or in a site where they are likely to be injured and possibly undergo malignant change. The removal of small moles is a normal procedure for most dermatologists or general surgeons, although large moles of this kind should usually be treated by a plastic surgeon.

Port-wine stains are often widespread, and such cases form one of the most disappointing groups of patients attending our out-patient departments. Over the years, I have tried reference to a plastic surgeon, used carbon-dioxide snow, combination of carbon dioxide with acetone, thorium X, soft X-rays, and so on, but the proportion of successes has been very small. It is just possible that with the passage of years, dermabrasion may prove helpful in a number of cases. So far, all treatments tend to lead to scarring, which may be worse than the original blemish. A very large proportion of the patients have half of the forehead, nose, cheek and chin involved, and some an upper limb (two patients of mine have involvement of half the body surface), thus very little treatment is practicable and safe for such cases.

Spider nævi do not usually disappear, but respond very well to treatment with electrolysis or actual cautery. Occasionally even carbolic acid applied on the pointed end of a matchstick produces quite satisfactory results, although I would not recommend this approach for lesions on the face or neck.

A considerable proportion of babies with ichthyosis tend to develop endogenous eczema and, in adult life, contact dermatitis. The general practitioner can do a great deal for the baby suffering from this disorder as, with proper care and prophylaxis, he may never become a patient suffering from eczema and dermatitis. When the skin is not active, as in the winter in cold climates, bathing with water must be limited to sponging the armpits, groin and feet, and the rest of the body massaged gently with an inert preparation such as arachis oil, olive oil, or a mixture of these with glycerin, anhydrous lanoline or vanishing cream base, &c. There is great value in adequate but not prolonged or excessive doses of vitamins A, B, C, and D for keeping the skin healthy.

Bath water can be softened by the use of bran with 3% emulsifying wax in water. In the summer these precautions are less necessary. Unless the skin is cracked and raw, do not discourage paddling or bathing when the age and opportunity arrive.

If the child with such a skin becomes fractious, rubbing his hands on legs or face, it is very important to ensure adequate sleep and sedation. If it is obvious that an eczematous reaction is starting, relieve irritation by the use of weak anti-pruritic sedative lotions, or tar and lead lotions. Various hydrocortisone preparations have proved to be a boon in many cases. Here it is a matter of experimenting with different types of bases and solutions. Dermatologists are constantly giving clinical trials to new mixtures. In certain cases, general ultraviolet light therapy, extra vitamin D, and so on, are certainly beneficial, and in others, addition of the vitamin B group to this seems to help. Always remember the danger of too frequent change of medicament, or too strong an anti-pruritic. Again, discourage vigorous cleansing of the skin with oil to remove ointment or picking of adherent crusts, as such over-enthusiastic treatment may prolong the disorder.

Assessment of the value of these procedures is extremely difficult because, as the child grows older, the endocrine glands take on their separate roles, the mind is more occupied by schooling or the influence of other children and sometimes the skin improves without any treatment, as one can see from comparatively neglected children seen in out-patient departments.

The rarity of certain disorders tends to make us less "aware" and alters the threshold level of diagnosis so it is wise to record at once "unusual" even though not diagnosable. Such clinical honesty often pays a dividend.

It is well to be suspicious of a child who appeared perfectly healthy at birth and who develops a measly rash, fractiousness and runny nose in association with loss of weight, as further investigation may reveal that the child is suffering from congenital syphilis. The nasal discharge may be hæmorrhagic, or again, the child's skin may be shrivelled and greyish with bullæ on palms and soles. At a later stage, the picture follows that of syphilis in adult life, with the gradual development of infiltrated lesions on the palms and soles, coppery rash and so on.

It has been pointed out to me by one of my clinical assistants that frequently we have to decide if patients with a skin disease can be inoculated or vaccinated and with what risk.

The majority of such patients can be vaccinated, but make an exception of those where an active eczematous eruption is present. There is no doubt that vaccination has acted as a trigger factor in the development of eczematous eruptions in certain patients. If an active eruption has subsided it is a question of where they are going to live, and whether quick vaccination can be procured if cases of smallpox occur in their district. They cannot postpone vaccination if they are proposing to proceed to Africa or other countries where smallpox is very common.

Mr. D. N. Matthews: The surgical management of many congenital malformations is the responsibility of the plastic surgeon, and it is essential that there should be close liaison between him and the general practitioner. The arrival of a malformed child in a family creates at once psychological and emotional problems for the parents and the other children. Similar problems confront the affected child as it grows older.

In the parents there is often a sense of guilt and shame, which can be dispelled by simple, patient explanation of what can be done, the right age at which to do it, the time it will take, and the scope and limitations of treatment. The sooner the parents receive this help the less will be their distress. The plastic surgeon should, therefore, see the child as soon as possible, and formulate as complete a plan of treatment as is practicable. He must also consult with the general practitioner, who will inevitably be asked many questions by the parents, no matter how carefully the specialist explains matters. Older children will benefit greatly if they are treated in the same way; their confidence and co-operation are gained at once. In formulating the plan, the plastic surgeon must take into account the harm done to the child by prolonged separation from its parents, and the increased difficulty such separation may cause the parents and the other children in accepting the deformed infant back into the home if normality cannot be fully restored. He must also pay attention to the added handicap the child will suffer if education is seriously interrupted, and should bear in mind the aid which other departments can offer. The Child Guidance Clinic, the Almoner, the special educational facilities at the disposal of the local health authority and the Probation Officer may all have important parts to play in adjusting the child through adolescence to adult society. But above all others, the general practitioner has the greatest influence in bringing the child and the rest of the family safely and happily through these difficulties.

The problems commonly confronting the plastic surgeon include clefts of lip and palate, birth-marks, moles, deformed ears and hands, ptosis and genital deformities. Each can only be touched on briefly in a general résumé of the subject.

Cleft lip and palate.—Clefts of the lip are repaired at about the age of 3 months, and necessitate ten days of hospital care. If the palate is cleft as well, the anterior part and the nostril floor are repaired at the same time. The rest of the palate, or the whole palate if the lip is intact, is usually repaired at the age of 15 months and necessitates between two and three weeks in hospital. In most cases, the primary repair of the lip is permanently acceptable, but in some cases revision of the scar, perfection of the cupid's bow or adjustment of the nose tip or alar cartilage are needed (Fig. 1A, B). These soft tissue corrections



A B

FIG. 1.—Secondary correction of hare-lip deformity: elevation of the nose tip.

can be made at the age of 3½ years, thus giving ample time for scar lines to fade before school age. The corrections rarely need more than one operation in all, and necessitate hospitalization for two weeks. In complete bilateral clefts, fullness may have to be added to a tight upper lip and is provided by the over-full lower. This can be done any time over

the age of 4 and takes about a month to do. If the bony framework of the nose is deformed, there are advantages to be gained by leaving this until the nose is fairly fully grown to avoid subsequent retardation. 12 to 14 years of age, depending on the size of the child, is satisfactory, and the procedure, which is similar to a corrective cosmetic rhinoplasty, takes two weeks.

If speech is not developing satisfactorily by the age of 8, improvement can be made in suitable cases by an operation on the pharynx (pharyngoplasty). This necessitates about two weeks of hospitalization. It is after such operations that the speech therapist is of the greatest help. Finally the orthodontist has a most important part to play in all clefts of the palate by assisting the expansion of the maxilla with spring-loaded appliances between the ages of 7 and 14.

Birth-marks.—These are red marks in the skin. They occur more commonly on the head and neck than elsewhere, and are of several different clinical types. The flat pink capillary lesion is the most likely to fade spontaneously and can be safely watched unless it is growing out of proportion to the overall growth of the child. The first sign of fading is usually the appearance of scattered white areas in it. These gradually extend and coalesce. If such a lesion fails to fade, it can be made to do so in most instances by surface applications of beta rays exhibited either as isotopes or as a radium plaque, or by carbon-dioxide snow. Raised cavernous lesions, which can be squashed flat by pressure, are more serious since they can grow with great rapidity and become formidable operative problems; if therefore they are progressing or fail to begin to regress after being stationary for a few months, they should be treated as emergencies. Shrinkage can frequently be induced by the injection of sclerosing agents such as saturated saline or by interstitial diathermy or a combination of the two. Great care must be exercised when using saline or a slough can easily be caused. Sclerosis may avoid the necessity for any operation, and will always reduce its magnitude. Treatment of these lesions can be begun safely in very young infants, and delay on account of age is wrong. It is nearly always possible to formulate a complete plan of treatment as soon as it is decided that action needs to be taken. Pulsating arterial lesions always need surgical excision.

Moles.—Pigmented lesions can only be satisfactorily treated surgically. Their removal is requested on cosmetic grounds or for fear of malignancy. Whilst it is true to say that malignancy in childhood is excessively rare, it is impossible to deny the possibility of malignant change in adult life. A request for removal on this ground is nearly always founded on a known tragedy in an adult, and it is unwise to refuse it. The technical requirement will be decided by the site and size of the lesion, and will vary from simple excision and suture to elaborate plastic repair. There is no evidence to support the fear that interference may promote malignancy.

Deformed ears.—The simplest deformity is an accessory auricle. It can be removed under brief anæsthesia in early infancy, and necessitates at most one night in hospital. There is nearly always a small cartilaginous element beneath the skin nodule, which must be taken away as well to prevent its subsequent growth.

Bat ears are the commonest of the deformities of the auricle, and are satisfactorily treated at 4 years or any age after this. The operation is done from behind the ear and necessitates ten days in hospital (Fig. 2A and B). Attempts at correction by positioning the infant in



A B

FIG. 2.—Bat ears. Correction by modelling the cartilages through a post-auricular incision.

the pram or by wearing a close-fitting cap are useless. The deformity often has a profound psychological effect on a school child, particularly a boy, and is well worth correcting.

Absence of the pinna presents a complicated problem of reconstruction, and no matter what is done, the result will fall short of perfection. It is well worth doing, however, particularly in a boy. It necessitates four or five operations. The interval between the first and the second should be two months as a minimum. The second, third and fourth stages are done consecutively and take nine weeks in all. The fifth takes two weeks and can be done a month after the fourth. In bilateral cases, it may be desirable to fenestrate one side to assist hearing. In girls a smaller procedure to provide the lower half of the pinna can be done in two stages.

Deformities of the hand.—These are of an infinite variety, and a plan has to be worked out for each. There are many for which little can be done. The primary concern must always be to improve function. Improvements in appearance are secondary to this. Appearance can often be helped by fitting a prosthesis worn as a dress hand on special occasions, but this should not be done until the child becomes self-conscious and asks for some disguise. In early childhood, it is imperative that the parents overcome their natural inclination to hide the deformity and encourage the child to use the hand as fully as possible. It is remarkable how little limitation quite a serious deformity ultimately imposes on the child if the problem is approached in this way. Little can be done surgically until the child is at least 3, and treatment may have to be postponed longer still to allow bony growth to occur.

Simple deformities, such as syndactyly, are readily amenable to surgery and are best tackled when the child is about 4. One or two operations may be needed, each necessitating a fortnight in hospital.

Ptosis.—Congenital ptosis may be unilateral or bilateral, partial or complete. Most cases show some improvement up to the age of 2 years. All show temporary deterioration through childhood during illness, fatigue or emotional stress. It is best to wait before repairing the deformity until the child is 2 years old. Operation is successful at any age after this. In bilateral complete cases, the child is virtually blinded by the lids, and interference is necessary when the child starts sitting up, but in this event a further secondary procedure is often required at 2 years. The results of surgery are excellent. The operation is performed from inside the upper lids and in bilateral cases is best done in two stages. Each stage necessitates ten days' hospitalization and the two can be done at one admission, totalling three weeks. The epicanthic fold, which often accompanies ptosis, is repaired at the same operation.

Genital deformities.—Hypospadias is the commonest and is not accompanied by incontinence, no matter how far back the opening is placed. It is best, therefore, to wait for normal continence to develop before operating. The repair is made in two stages, each taking about a fortnight with a minimum interval of three months between them. Treatment is usually undertaken when the child is between 2 and 3 years old.

Epispadias is more serious since in many cases it is accompanied by lack of sphincter control. When the deformity extends upwards from the urethra to the abdomen, the condition of ectopia vesicæ results. Epispadias is a lesser degree of the same malformation. In some a reasonable amount of control can be achieved, but in the larger and longer clefts, as in ectopia vesicæ, it is often impossible. Much work has been done and some progress made towards solving the technical problems which this deformity presents, but in many cases ureteric transplantation into the colon is still the best procedure.

The ectopic opening of the anus into the posterior vaginal wall, which is a commoner malformation than might be supposed, can be corrected with good sphincteric control in most cases.

Section of Medicine

President—G. E. BEAUMONT, M.A., D.M., F.R.C.P., D.P.H.

[*April* 30, 1957]

DISCUSSION ON AORTIC STENOSIS

Dr. Raymond Daley:

Little advance has been made in the basic understanding of naturally acquired valvular disease since the classical observations of Corrigan in 1832, who described the dynamics of regurgitation, and of Hope in 1835, who noted "the small, weak arterial pulse of aortic stenosis while the heart is giving a violent impulse".

The ætiology of aortic stenosis is often not clear either on clinical or histological grounds. It is a pity that some writings in the past have been so dogmatic in stating that juvenile rheumatism is the cause of the lesion in almost every patient. Congenital aortic stenosis is an important disease with considerable possibilities of surgical improvement. I believe that a number of patients suffer from arteriosclerotic stenosis and there are, of course, a few rare causes such as fibro-elastosis. The historical evidence of rheumatism or chorea in 50 of our patients is less than 50% but a history of rheumatism is a little more common in females than in males. At post-mortem 20 patients had rheumatic aortic stenosis, 6 had congenital lesions, but in 24 it was not possible to give a firm ætiological diagnosis.

Leonardo da Vinci (1513) was the first to show the normal aortic valve opened to give a triangular orifice.

McMillan (1955), working in our Department at St. Thomas's Hospital, has studied a number of fresh post-mortem aortic valves by cinematography. He has shown that as long as the free borders of the cusps are mobile and shut well there may be considerable calcification in the peripheral parts of the cusps and walls of the sinuses of Valsalva without limitation of flow in the valve area. Some fusion of the peripheral parts of the commissures can occur without causing symptoms. Out of 30 specimens studied the shape of the orifice could be roughly divided into certain groups which are:

(i) Early peripheral fusion with good function centrally (3 cases).
(ii) Peripheral calcification not affecting function (1 case).
(iii) Fusion of one commissure (14 cases).
(iv) Partial or complete fusion of two commissures (5 cases).
(v) Partial or complete fusion of three commissures, often with incompetence, and
(vi) Cone-shaped valve with an ellipsoid orifice at the apex, and no sign of former commissures.

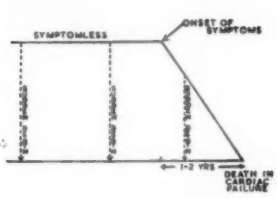


FIG. 1A.—Aortic stenosis.

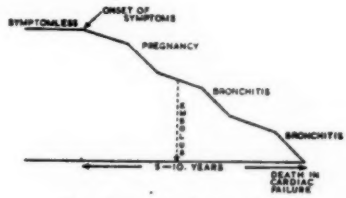


FIG. 1B.—Mitral stenosis.

The life-history of the disease differs significantly from that in patients suffering from mitral stenosis (Fig. 1). The patient is more likely to be male, and in his late forties. He is unlikely to have had serious symptoms for a long time. Once they have developed the first hospital admission may well be the last. Grant (1933) has studied the after-histories

of 43 men with aortic stenosis and incompetence for ten years. 15 died during this time. Two of the most striking features are the considerable liability to sudden death and the comparative rarity of auricular fibrillation.

Apart from left ventricular failure the two most interesting symptoms of aortic stenosis are effort syncope and angina pectoris. Angina occurs in about half the patients and is particularly prevalent in young women. The cause of the pain seems to be quite clear. Left ventricular work is greatly increased, the mean coronary filling pressure reduced, the cardiac output fairly small and fixed, and diastole is shortened. I think that it is a little unnecessary to invoke a sucking action at the coronary ostia due to the jet of blood entering a dilated ascending aorta.

The mechanism of effort syncope is not clear. I doubt if it is due to an arrhythmia, although presumably ventricular fibrillation is the cause of sudden death. Syncope can be initiated by emotion, effort and heat in anyone with a fixed cardiac output. Although the blood flow tends to be low and rather fixed, effort syncope is uncommon in mitral stenosis and hypertensive heart failure, because the blood pressure does not fall. In the former, chronic pulmonary capillary congestion exists, leading either to immediate disabling pulmonary symptoms or to reflex systemic vasoconstriction. In the latter the systemic vasoconstriction is not readily released on effort. Effort syncope, however, is not uncommon in primary pulmonary hypertension. The minute output again tends to be fixed but the blood pressure falls on effort, presumably when muscle vasodilatation occurs, because there is no pulmonary capillary congestion to inhibit its occurrence. Perhaps dilatation can be similarly initiated in aortic stenosis because of the normal and only slowly rising pulmonary capillary pressures. In 2 patients suffering from aortic stenosis whom I have observed fainting there was a bradycardia and the episode appeared to have the quality of a vasovagal attack.

I do not wish to dwell on the physical signs but I should like to make a plea for the abandonment of attaching diagnostic importance to the presence or absence of a systolic thrill in the aortic area. It is surely more sensible to feel the carotid arteries or the aortic arch at the root of the neck. Coarse vibrations felt there are diagnostic of aortic stenosis and are quite unlike the smooth thrill felt in an aortic to-and-fro murmur due to predominant aortic incompetence. The hearing of the murmur over the olecranon processes is no more than a clinical *tour de force*. If the murmur is loud enough it will have wide radiation. An important point to recognize is that if aortic stenosis is very severe blood flow may be insufficient to produce a murmur. This is sometimes seen in the operating theatre, when pressures are simultaneously measured in the left ventricle and aorta. If the cardiac output is sufficiently reduced there may be no pressure gradient across an aortic stenotic valve. A useful sign is an early systolic click associated with post-stenotic dilatation of the ascending aorta.

Valve calcification (Fig. 2) is very common although I know of no means of assessing

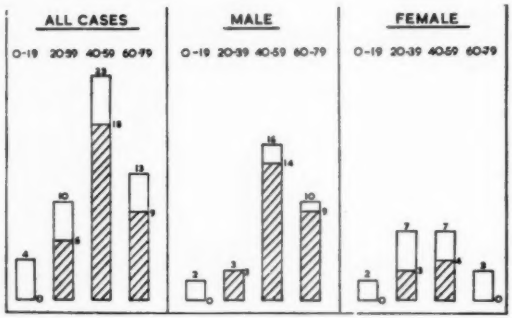


FIG. 2.—Calcified valve in aortic stenosis.

whether it is in the valve or the valve ring. It is best seen with the image intensifier but ordinary fluoroscopy is so satisfactory that if it had been invented after tomography it would have been hailed as an advance.

A great deal has been said about pulsus bisferiens in combined aortic stenosis and incompetence. It may be a very useful sign but varying pressure of the palpating finger may give the impression of pulsus bisferiens where none exists. The most important

measurement in the peripheral pulse is delay in the systolic upstroke time. This is prolonged to between 0·175 and 0·3 second in five cases of aortic stenosis (Fig. 3) and may revert to normal after successful valvotomy.

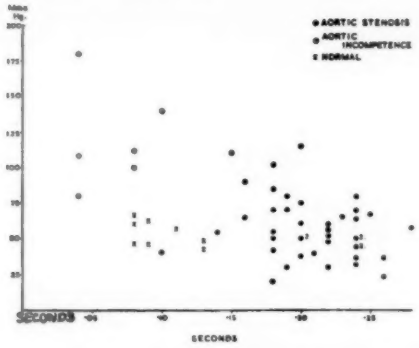


FIG. 3.—Brachial artery pulse pressure and systolic upstroke time.

In 1955 Gorlin joined us at St. Thomas's Hospital in a hæmodynamic study of a number of patients with aortic valve disease. Some of the deductions were made by a combination of cardiac catheterization and study of other hearts in McMillan's artificial perfusion system. With the advent of direct left ventricular puncture either through the chest wall as Brock practises or via a bronchoscope and the insertion of a fine polythene tube as we have been doing, these deductions have been found to be substantially correct. They are that:

The "critical" orifice area in pure aortic stenosis is 0·5 sq. cm., in mixed stenosis and incompetence less than 1·5 sq. cm. With these respective degrees of stenosis left ventricular systolic pressure is elevated to 200–250 mm.Hg with transvalvular pressure gradients of 100–150 mm.Hg. Because of the inability of the coronary flow to increase in proportion to the demands of ventricular work, due to low coronary perfusion pressure, the ventricular systolic pressure seldom exceeds 250 mm.Hg when no further stroke work can be done. In view of the large gradient between the aorta and ventricle in diastole, regurgitant orifice areas no greater than 0·5 sq. cm. were capable of more than doubling total ventricular output and work. Although left ventricular stroke work is increased at rest (two to four times normal) the pulmonary capillary diastolic pressure is near normal in 80%.

There are four stages of the disease:

Stage I: The valve orifice area is greater than 0·5 sq. cm. in pure cases and greater than 1·5 sq. cm. in mixed cases. The only physiological deviation will be a prolonged systolic upstroke time. The patient is free of symptoms.

Stage II: The valve orifice area is 0·5 sq. cm. or less in pure cases and less than 1·5 sq. cm. in mixed cases. Resting left ventricular diastolic pressure and blood flows are within normal limits, but on effort the diastolic pressure rises. Stroke output and work are fixed. These patients are free of symptoms except with unusual but varying degrees of effort. The limitations here are mainly hydraulic in nature.

Stage III: Orifice areas are the same but the myocardium usually shows signs of generalized patchy fibrosis from years of impaired coronary flow. The huge load borne well in Stage II is no longer tolerated on slight exercise. The resting left ventricular diastolic pressure is within normal limits or elevated slightly and blood flow is invariably decreased. Effort causes elevation in diastolic pressure, a fixed or falling output, and often acute right ventricular failure as well. These patients are limited by symptoms, first of left- and soon of right-sided failure. Thus it is not until late in the disease when the muscular component fails that symptoms become severe and the disease runs an accelerated course.

Stage IV: Terminal bilateral cardiac failure.

I should like to submit that patients should be operated upon while still in Stage II, before serious symptoms and myocardial fibrosis have appeared. This means that the majority of patients will be children and young people in whom gross valvular calcification has not yet occurred. The best operative results appear to be in young people with non-calcific congenital aortic stenosis. The worst results are in middle-aged patients in whom the valves are usually heavily calcified. It must be stressed again that any blind procedure

which leads to increased incompetence even with some lessening of stenosis is a disservice to the patient.

If operation is decided against, apart from the usual medical measures thyroid ablation is often worth while. It is best carried out with radio-iodine. Following treatment, angina is usually much improved, dyspnœa is less and sometimes the heart size decreases.

I have deliberately avoided discussing subaortic stenosis because, despite what people tell me, I believe it is a very rare disease and its diagnosis inaccurate.

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Mr. Andrew Logan (Department of Surgery, University of Edinburgh):

The Surgery of Aortic Stenosis

The views which I shall express on the surgery of aortic stenosis are based on an experience which is small in relation to some of the published figures. For example, Bailey (1956) quoted 450 cases of aortic valvotomy and Harken (1956) 70 cases. I have performed aortic valvotomy in only 31 cases. 7 of the patients had congenital aortic stenosis; 17 had acquired aortic stenosis without significant incompetence or other valvular lesion; and 7 had aortic stenosis combined with mitral stenosis.

The records of the first 6 patients with congenital stenosis have already been published (Marquis and Logan, 1955). Each underwent pre-operative angiocardiography in an attempt to exclude subvalvular stenosis since it seemed inappropriate to attempt enlargement of a subaortic ring by the same technique as was used for the separation of fused cusps. All were operated upon more than three years ago. None has died. In all, the signs of aortic stenosis were reduced. In 5, however, aortic incompetence was produced or increased, and in 2 the incompetence was severe. The single patient who had no reflux after operation still has none and is well. The result in her case is good enough to indicate that the aortic cusps were flexible and well-formed and that valvotomy achieved extensive separation of the cusps accurately in the line of the commissures. The occurrence of slight to severe, but not lethal, aortic incompetence in the other 5 cases, along with a reduction of stenosis, suggests that in these, too, considerable separation of the cusps in the correct line was obtained, but that the cusps were ill-formed rather than that a cusp was divided at operation. The most severe incompetence occurred in a boy of 13. He still has severe incompetence and the heart is larger than it was 6 months after operation, but whereas he was, at 13, a weedy boy 14 lb. underweight he is now, at 16, 3 st. heavier, up to normal weight, asymptomatic and leading an energetic life. In all, an improvement in cardiac function and in general health has lasted for three years after valvotomy. It remains to be seen how long the heart will compensate for reflux before a comparison can be made with the calculated effect of unrelieved stenosis. Meantime, there is no reason to change the opinion that valvotomy for congenital aortic valvular stenosis should be reserved for those patients who are in danger of sudden death or of deterioration which might prejudice the outcome of a later operation. The risk of incompetence does not justify withholding operation in growing children who show the electrocardiographic pattern of extreme left ventricular hypertrophy and in adults who show progressive left ventricular hypertrophy with increasing cardiac size.

The seventh patient in the congenital group was not investigated by angiocardiography. At that stage it was assumed that severe aortic stenosis was almost certainly valvular and not subvalvular. Inspection of the heart at thoracotomy raised no suspicion that the stenosis was subvalvular. The same blind transventricular approach was used. It was immediately obvious that a different condition had been encountered because the obstruction, instead of being disrupted with ease, strongly resisted the opening of the dilator. I exerted a degree of force quite inappropriate to valvotomy and succeeded in widely opening the dilator. There was no thrill of reflux or evidence of other damage and the heart's action remained good. The state of the child gave no cause for anxiety until sudden death occurred five hours later. At autopsy a fibrous ring was found 0·7 cm. below the lowest part of the aortic cusps, which were normal. The ring had been ruptured posteriorly and

the tear which extended into the ventricular wall passed upwards in the aortic wall between the right and left posterior cusps, then above the left coronary orifice. None of the cusps was damaged. Death may have been the result of obstruction of the mobilized left coronary orifice although there was no pathological evidence that obstruction had occurred.

The 17 patients with acquired aortic stenosis and no other major valvular disease were selected in the belief that the duration of their survival without operation was likely to be less than eighteen months. The records of some of these also have been published (Logan and Turner, 1954). All had more than one of the triad, syncope, angina, and congestive heart failure. Only 2 had uncalcified valves.

Of these 17, 9 are dead, 1 during operation, 3 within three weeks of operation, and 5 from six to thirty months after operation. The immediate death was the consequence of neglect of the elementary precaution of controlling the ventricular incision with a tourniquet. The search for the orifice among the calcific masses of the valve was more prolonged than usual, blood leaked continuously, ventricular fibrillation supervened and normal rhythm could not be restored. Of the 3 early deaths, 1 was from pulmonary infarction three days after operation. The patient had intractable cardiac failure for which a year before I had ligated the inferior vena cava. She had a severe degree of hepatic cirrhosis. One patient died nine days later from coronary thrombosis with a large cardiac infarct. 2 of the patients who died later had been temporarily improved and the others followed the uninterrupted course of severe aortic stenosis. 2 were examined *post mortem*. Both had rigid valves, one without evidence of division. One heart weighed 900 grams and the other 1,100 grams.

Of the 8 survivors, 1 did not have a valvotomy because I was unable with the maximum permissible force to rupture a calcific ring surrounding the valve orifice. All the others have some increase of aortic reflux. One has a left homonymous hemianopia, the result of calcific embolism. Because of a technical difficulty the head vessels had not been occluded during valvotomy. One is not obviously improved. 5 have lost their important symptoms and follow normal activities. One is asymptomatic. Pre-operatively he was dyspnœic and suffered from angina and syncope. He had been in congestive heart failure. For five weeks after operation he remained in heart failure but three months later returned to office work and has remained well for three years.

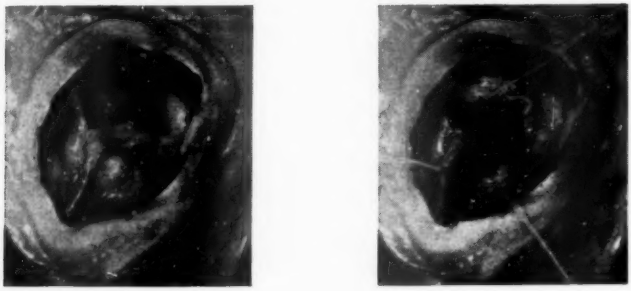
That is, in 17 cases of acquired aortic stenosis there were 4 early deaths, 5 late deaths, 2 unimproved and 6 with improved cardiac function, one of them much improved. None had a severe degree of aortic reflux.

The 7 patients with combined aortic and mitral stenosis were all initially improved. None died and none had severe aortic reflux. Since the gradient across the aortic valve was not measured, I have no means of apportioning the benefit to the two operations or of indicating how the aortic valve was affected.

If the selection of cases of aortic stenosis for operation is restricted to those in which cardiac impairment is so severe that death is imminent, the question arises whether surgical intervention by blind valvotomy is profitable. The opinion has been given that we merely deduct a few months from one patient's life and add them to that of another without a net gain. Taking the worst group, that of pure acquired aortic stenosis, that is clearly not so. In the whole group there were few years to come and all of them bad. There have already been three good years and ten fair years, which compares well with the results of the surgery of carcinoma.

The technique used in all cases was the same. Through a left thoracotomy a two-bladed expanding dilator with a spread of 4 cm. was introduced through an incision in the anterior wall of the left ventricle and placed in the aortic valve under the guidance of external palpation of the origin of the aorta. The dilator was opened as far as that could be done with a reasonable amount of force or until the aortic wall was stretched over it. Then the dilator was withdrawn and the ventricular wall was repaired. This is an exceedingly crude method of valvotomy but I can say that by the use of a similar technique in mitral stenosis the commissures are more often and more completely divided, and with less damage, than I can achieve by any other way. The dilator sometimes selects a commissure when I am unable to recognize it by digital palpation. It is at least possible that the same would be true in aortic stenosis. The absence of sudden severe post-operative aortic incompetence suggests that in none was a cusp completely divided. I am unconvinced of the need for a three-bladed dilator or of the likelihood that the blades will occupy the commissures. Again comparing the mitral operation, the valvotomy is simply a matter of tearing by stretching and, whatever the direction of the stretch, the tear occurs in the weakest line which is fortunately usually the commissure. The amount of force required to tear a cusp is so great as to be easily recognized and avoided. If the aortic cusps are malformed or destroyed no technique at present available will make their function good

If the cusps are well formed the dilator will probably separate them as effectively as any other instrument (Fig. 1A and B).



A B

FIG. 1.—Acquired aortic stenosis without calcification after valvotomy. A, Valve closed; B, Open. The appearance of rigidity is the consequence of fixation. In the fresh state the cusps had almost normal mobility.

Bailey (Bailey *et al.*, 1956) began to approach the aortic valve through the ascending aorta for two reasons: because he had encountered ventricular fibrillation with the trans-ventricular route, and the thick friable ventricular wall had sometimes been difficult to repair. He did not by the change eliminate trouble from ventricular fibrillation and bleeding but continued to use the trans-aortic route for the sake of avoiding injury to the ventricular muscle and of using the finger both for the performance of the valvotomy in some cases and the assessment of the quality of the valvotomy in all. I believe that the expanding dilator usually makes a less traumatic valvotomy than the finger because each blade provides counter-pressure for the other, whereas the finger must pull upon the pedicle of the heart or against externally applied pressure. Digital palpation of the valve after valvotomy would certainly be helpful in prognosis and might sometimes lead to modification of the state of a commissure after the first dilatation. Whatever route is used, ventricular fibrillation is likely to occur in some cases. The massive thickness of the left ventricle and the small left ventricular cavity make effective cardiac massage, as judged by the presence of a radial pulse, difficult or impossible and electrical defibrillation must be used without delay.

With the increasing use of refrigeration and of pump-oxygenators to permit open cardiotomy in other conditions it is to be expected that they should be used for aortic valvotomy under vision. In the United States, Lewis *et al.* (1956) and Swan (1956) have used refrigeration and Lillehei *et al.* (1956) the pump. In the short time afforded by refrigeration I doubt that with knife or scissors I could make as accurate a dissection of the commissures as competence of the valve demands, even in an uncalcified valve with well-formed cusps. Where the cusps are deformed or the commissures obscured or calcified I should prefer to rely on the dilator for their separation. For the division of a subaortic stricture, however, a visual approach may be desirable and the three to five minutes afforded by refrigeration may be adequate for this. Probably neither refrigeration nor the pump-oxygenator is necessary for the correction of aortic valvular stenosis so far as that can be done now, just as they are unnecessary for the correction of mitral stenosis. But the visual approach through the aorta with the pump-oxygenator has importance for the future since it will be by that method that the aortic valve will be assessed and repaired or replaced by a prosthesis when an efficient and durable one can be constructed.

It is clearly important in cases of congenital aortic stenosis to know pre-operatively the site of stenosis. For this purpose some reliance has been placed on angiocardiography although evidence that it would demonstrate a subaortic stricture is lacking. Some help might be derived from manometry of the left side of the heart by left ventricular puncture as practised by Brock *et al.* (1956). In manifestly severe acquired aortic stenosis measurement of the systolic gradient across the aortic valve before operation cannot contribute much. If, as is likely, the maximum opening of the valve is completed with one dilatation, measurement of the gradient during operation, before and after valvotomy may aid prognosis but nothing else. When aortic stenosis complicates mitral stenosis, however, measurement of the gradient across the aortic valve after mitral valvotomy is required for the decision on proceeding to aortic valvotomy. For lack of that investigation I have on two occasions

omitted aortic valvotomy at the time of the mitral operation and been obliged to repeat the thoracotomy a few months later. The principal value of pre-operative measurement of a pressure gradient and blood flow at the aortic valve is probably in the assessment of patients who, having undoubted aortic stenosis and left ventricular hypertrophy are yet asymptomatic and have little valvular calcification. It is in this group that the best result from valvotomy is to be expected but the prognosis is so uncertain that the achievement by operation cannot be estimated. There is no obvious way of overcoming this difficulty but to find a large enough number of these cases by routine cardiac examination and, having overcome hesitation to use ventricular puncture in asymptomatic patients, to select an arbitrary degree of severity of stenosis as indicated by the integration of pressure gradient and blood flow at the aortic valve; then, rather than operate on all with more severe stenosis (a course which could give information only about the undesirable consequences of valvotomy) or continue to observe the natural course in all, to make control series for operative and conservative management.

Summary

(1) Although the results of aortic valvotomy in patients who have been gravely damaged by aortic stenosis are poor they are worth while.

(2) The blind transventricular operation probably gives a valvotomy as accurate as other methods but the trans-aortic route must be expected to be required in due course for replacement of the valve.

(3) In symptomatic pure aortic stenosis, measurement of the pressure gradient across the aortic valve during thoracotomy can contribute to prognosis but in combined aortic and mitral stenosis it may be necessary for a decision on the need for aortic valvotomy.

(4) The use of aortic valvotomy should be extended to asymptomatic patients investigated by measurement of the pressure gradient and blood flow across the aortic valve and known to have severe stenosis, but an attempt should be made to compare the prognosis with and without valvotomy.

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Dr. J. F. Goodwin (speaking at short notice in place of Professor J. B. Duguid):

I propose to discuss the study of aortic stenosis by means of the cardiogram and arterial pulse tracing, and wish to present the results of some work (with which I have been closely associated) by my colleagues, Drs. Abdin, Doyle and Neilson, at the Postgraduate Medical School.

Abdin (1957) has studied the cardiograms of 53 cases of aortic stenosis (25 of whom are living), and compared them with 19 cases of coarctation of the aorta, 15 cases of hypertension, and 4 cases of hypertension associated with ischæmic heart disease. Deep T-wave inversion (greater than 5 mm.) in left præcordial leads was found in 26 of the cases with aortic stenosis, but in only one of the hypertensive and coarctation cases respectively. By contrast, it was found in 3 of the 4 cases with ischæmic heart disease and hypertension. T-wave inversion was found to be appreciably greater in cases of aortic stenosis than in those with hypertension who had equal R-wave voltage, and equivalent degrees of left ventricular hypertrophy at autopsy. This disproportionate T-wave inversion suggested that some factor other than myocardial hypertrophy was responsible, and the finding of ischæmic lesions in the myocardium in the absence of coronary artery disease in 13 cases of aortic stenosis at autopsy suggested that this factor was cardiac ischæmia, which results from deficient coronary blood flow due to the obstruction to the outflow of the left ventricle. The presence of very similar degrees of T-wave inversion in the cases with ischæmic heart disease and the known association of anginal pain with aortic stenosis harmonize with

this view. In 6 cases of aortic stenosis and 3 of hypertension an **RS** pattern was found in V_5 in association with signs of left ventricular hypertrophy. All had pathological evidence of right as well as left ventricular hypertrophy, supporting the findings of Pagnoni and Goodwin (1952).

Doyle and Neilson (1957) have studied the relation of the systolic upstroke time of the peripheral arterial pulse to the pulse pressure in aortic stenosis with and without incompetence. In aortic stenosis the systolic upstroke is usually prolonged and the pulse pressure usually low, but close correlation with the severity of the stenosis is often not obtained. When the pulse pressure was related to the upstroke time during changes induced by the Valsalva manœuvre, or during atrial fibrillation, cases of severe stenosis showed a considerable reduction in upstroke time for a given change in pulse pressure. In mild cases and in those with significant associated incompetence, there was little change in upstroke time for an equivalent change in pulse pressure. The reduction in upstroke time in relation to fall in pulse pressure was considerably less after successful aortic valvotomy. Expressed in another way, patients with severe aortic stenosis showed little alteration in rate of rise of the systolic upstroke during the Valsalva manœuvre, while those with incompetence showed considerable alteration. The fall in pulse pressure during the Valsalva manœuvre is probably due to a fall in stroke volume, and hence the marked reduction in upstroke time when the pulse pressure falls suggests that the systolic upstroke time is a resultant of the stroke volume and resistance at the aortic valve. The form of the arterial pulse in aortic stenosis is mediated, at least partly, by changes in peripheral resistance, since pulses of equal size recorded at various stages during the Valsalva manœuvre were often of different contour.

Measurement of the systolic upstroke time in relation to changes in the pulse pressure in a number of cardiac cycles offers a better guide to the severity of stenosis than measurement of the resting tracing.

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Mr. W. P. Cleland said that he had performed aortic valvotomy on 15 patients during the last three years. In only 1 of these was the ætiology believed to be congenital. In 9 there was pure calcific aortic stenosis, and in 5 there was mitral valve disease in addition to the aortic stenosis. All these patients belonged to Dr. Daley's Stage III.

He would entirely agree with Dr. Daley that his Stage II cases were likely to give better results with surgical treatment, but he disagreed that the Stage III cases should not be submitted to operation, as the follow-up of his own small group indicated.

Of his 15 patients, 3 died either at operation or in the immediate post-operative period—2 from cardiac arrest and 1 from a calcific cerebral embolus.

Of the survivors, only 1 has died. The remainder have been followed-up for periods of six months to three years and all have maintained their original improvement.

The majority of the patients had symptoms of angina, syncopal attacks and dyspnœa, and considerable relief of symptoms was obtained in the majority. This improvement was associated with equivalent objective signs of benefit.

The transventricular approach was employed in all, using a triradiate mechanical dilator. Interference with the myocardium was reduced to a minimum and blood loss from the ventricle was very carefully avoided. Lack of attention to these two details was certainly responsible for two of the operative deaths.

The effects of the operation were determined by measuring the gradient across the aortic valve and by determining the systolic upstroke time of the pulse wave. The measurement of the gradient gives a valuable idea of the degree of obstruction and the amount of relief obtained, provided conditions at the time of successive measurements are as nearly similar as possible.

Mr. Cleland was quite satisfied with a 50% reduction in gradient even though the latter was still high. Repeated attempts at dilatation in an attempt to reduce the gradient often resulted in troublesome or fatal cardiac irregularities.

The follow-up of these cases has suggested that a fairly conservative approach is quite justified. He has not felt the need to approach the valve through the aorta but considers the performance of aortic valvotomy under direct vision in a bloodless field and a motionless heart is probably likely to be the operation of choice in the future.

Dr. Ronald Gibson said that at The Brompton Hospital and at Guy's Hospital, direct puncture of the left ventricle was performed in 60 patients. The results in the first 28 cases had been analysed in detail by Dr. Peter Fleming and himself (1957). The procedure was simple and safe, but the systolic pressure gradient across the aortic valve obtained by this method must be interpreted with caution. This gradient depended not only on the size of the valve orifice, but also on the stroke volume, which is related to cardiac output, heart rate and the degree of aortic regurgitation. For example, he had found that with an estimated valve size of 0·25 sq. cm. at operation the systolic gradient at left ventricular puncture varied between 30 and 210 mm.Hg. These results are considered to be due to differences in stroke volume. A gradient of up to 100 mm.Hg had been found with dominant aortic regurgitation. However, all cases with a systolic gradient of 120 mm.Hg or more had dominant aortic stenosis. There was, therefore, little correlation between height of a pressure gradient and the surgeon's estimate of the valve size. In the absence of significant aortic regurgitation there was a fair correlation between the surgeon's estimate of the valve size and the calculated aortic valve area. The left ventricular ejection period was prolonged in all cases, but degree of prolongation gave no indication of the degree of valve obstruction. Therefore they considered that paradoxical splitting of the second heart sound did not necessarily indicate severe aortic stenosis. On the other hand, it was found that the degree of prolongation of the corrected brachial upstroke time was related to the severity of the stenosis.

A direct relationship had been found between the systolic gradient and the degree of left ventricular hypertrophy on the electrocardiogram in all the cases in this series, irrespective of whether stenosis or regurgitation was the dominant lesion.

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Mr. Ian M. Hill:

I have carried out 12 aortic valvotomies in adults, 2 in isolated aortic stenosis and 10 combined with mitral valvotomy, all by the transventricular approach at normal temperatures.

The 2 isolated cases were severely disabled, 1 with right and left failure and the other with angina. The case with failure had a good result and now two and a half years later is beginning to slip back again. The anginal case died of irreversible ventricular fibrillation at operation, one mass of calcium in the valve producing partial rupture of the aortic wall when pressed against it by the dilator, leading to a hæmatoma about the origin of the left coronary artery.

Electromanometer pressure readings have been taken in all cases at operation; but the gradient across the aortic valve is not always helpful in assessing the degree of stenosis under these conditions as the operative handling of the ventricle may grossly alter the output and therefore the gradient across the valve. Usually after mitral valvotomy the aortic gradient increases, but where the left ventricle has been manipulated it may even fall despite a good mitral valvotomy. Direct sounding of the aortic valve through the apex of the left ventricle is a more reliable assessment and in the 10 cases mentioned and another 6 in whom the aortic valve was sounded, but not dilated during mitral valvotomy, there was no mortality and no morbidity in this method of handling the problem. The functional results have been good.

Mr. D. N. Ross said that Sir Russell Brock had performed about 130 aortic valvotomies (1957), mostly by the transventricular route with good results. He agreed with Mr. Cleland that there was danger in prolonged manipulations with the dilator in situ while trying to abolish the gradient entirely. This was likely to precipitate ventricular fibrillation. The overall mortality figures were approximately 10%, the figure being higher in the earlier cases and lower now.

In addition, he had operated on about 15 cases of congenital aortic stenosis under direct vision through the aorta with the aid of hypothermia.

There had been a surprising number of cases of subaortic stenosis encountered—about 11 cases or approximately 10%. At present there is no entirely satisfactory method of demonstrating this lesion pre-operatively and attempts had been made to do catheter withdrawal tracings via a LV puncture needle. The present attitude is that calcification of the

valve is so common in isolated aortic valve stenosis in patients of 30 years of age that subvalvar stenosis is suspected in any patient of this age who does not have a calcified valve on screening. At operation, in a suspected case, withdrawal pressure records are taken with a catheter and these show an "infundibular" type of tracing below the valve. Subvalvar stenosis is generally of a diaphragmatic nature—consisting of a ring of puckered endocardium about 1 cm. below the valve and this is split by means of blunt transventricular dilatation.

REFERENCE

BROCK, R. C. (1957) *Brit. med. J.*, i, 1019.

Mr. B. B. Milstein:

I should like to add two points which have emerged from Sir Russell Brock's experience. The first is the hopelessness of operating on patients in intractable cardiac failure from aortic stenosis. Such patients were submitted for operation early in his series and the mortality was extremely high. These cases are now rejected as beyond hope of surgical treatment. Patients who have been in right- or left-sided heart failure but who respond to medical treatment are not subject to the same operative risk and very good results have been obtained in these advanced cases but it is desirable to wait as long as possible, preferably three months after the attack of cardiac failure, before proceeding to operation.

The second point concerns the results of operation. This is not entirely a matter of duration of life after operation. Anginal pain and syncope, for example, can usually be completely relieved. The effect on exertional dyspnœa is variable. Some patients may die subsequently from left ventricular failure and this is not surprising when one sees the gross hypertrophy of the left ventricle and the extreme degree of fibrosis in the muscle which is present in advanced cases. These changes are clearly irreversible. Nevertheless, these patients' lives may be made tolerable by the relief of angina or syncope as a result of operation.

Dr. C. J. Gavey mentioned the value of the symptoms of weakness and ready exhaustion of fairly sudden onset, in drawing attention to the possibility of serious deterioration in the prognosis of aortic stenosis. Such symptoms were so often due to anxiety that there was a risk of overlooking their alternative origin in the falling cardiac output due to aortic stenosis.

Dr. Gavey stressed the difficulty of deciding whether or not to offer surgery in the more advanced valvular lesions, especially since certain mechanical estimations of function, however carefully performed, could sometimes be misleading.

Mr. I. K. R. McMillan said that he had carried on his investigation of the function of stenotic aortic valves beyond the figures quoted by Dr. Daley and that his experience now included some 50 cases. The classification of the type of orifice still fell into six main groups, which were as follows:

(i) Early peripheral fusion with good function centrally (4 cases).
(ii) Peripheral calcification, not affecting function (2 cases).
(iii) Fusion of one commissure (24 cases).
(iv) Partial or complete fusion of two commissures (8 cases).
(v) Partial or complete fusion of three commissures, often with incompetence (8 cases).
(vi) Cone-shaped valve with an ellipsoid orifice at the apex, and no sign of former commissures (3 cases).

He pointed out the risk in group 4 when doing a blind valvotomy of tearing the relatively normal commissure and producing incompetence while not splitting the fused calcified commissures, and suggested that direct vision surgery of the valve would be advantageous in these cases.

Section of Laryngology

President—J. ANGELL JAMES, M.D., M.R.C.P., F.R.C.S.

[*November* 2, 1956]

A Laryngologist's View on Allergy

PRESIDENT'S ADDRESS

By J. ANGELL JAMES, M.D., M.R.C.P., F.R.C.S.

"Quod cibus est aliis, aliis, est atre venenum."
(Latin Proverb).

"What is food to some is black poison to others."

It is very remarkable that in spite of the striking character and widespread distribution of allergic diseases no one seems to have studied them particularly until John Bostock (1828) of Guy's Hospital wrote a treatise on "Hay Fever" under the title of "Summer Catarrh".

If we accept the term allergy as meaning "altered capacity to react" the use of the word should be extended to include all forms of hypersensitive reactions, whether antigen antibody reactions have been proved to occur in them or not. Clinically the two types of reaction are indistinguishable and occur often in the same patient. I hope that this wide use of the word will be generally adopted.

PATHOLOGY

THE allergic reaction induced by histamine released in the tissues by the allergen antibody union shows five characteristic features:

(i) Vascular dilatation.
(ii) Loosening of endothelial cement and escape of fluid from the surface of the tissue.
(iii) Increased activity of the seromucinous glands.
(iv) Eosinophil infiltration, mostly in the subepithelial tissues, but also migrating through the surface to appear in the secretion.
(v) In the later stages after repeated attacks:
  (*a*) General hyperplastic thickening and œdema.
  (*b*) Massive localized œdema presenting as polypi.

INCIDENCE OF ALLERGY

There have been many surveys of the incidence of allergy in general and it appears that it differs from one country to another and also seems to differ in different classes and types of the same community.

For example, allergy generally would seem to be more prevalent in America than in England, while hay fever, which is common in England and America, is unknown in Japan.

The most important reasons for these differences are the variations in the intensity of concentration of allergens, and of stress and environmental factors in predisposing to allergy. In America there is an immense crop of ragweed which prolongs the pollinizing season, and hay fever afflicts the Japanese who have migrated there (Hara, 1939).

As an average figure it is stated by Vaughan (1934) that 10% of Americans are frankly allergic, and 50% give histories of transient episodes of minor allergy. Bray (1937) estimated that 10% of the British population were allergic.

I have investigated the number of allergic patients seen in the course of my practice over the years 1929 to 1939 and 1946 to 1956. In the first decade there were 593 allergic patients,

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in a total of 5,050 patients of all types: in the second decade there were 1,239 allergic patients in a total of 8,735 patients, giving a percentage of 11% allergic in the first and 14% allergic in the second decade.

The earlier writers were quite convinced that the incidence was greater in the more intelligent than in the less intelligent groups, but Piness and others (1937) have denied any significant difference. I am convinced that the level of intelligence is an important factor, for when I was investigating the nose, throat and ear conditions of 600 mental defectives over the course of several years at Stoke Park Colony, I did not find a single case of asthma or nasal allergy, and only one patient who had any suggestion of allergy, and that was a high grade moral imbecile with nasal polypi. This is in accord with the findings of Leavitt (1943) who did not discover a single case of asthma among 5,000 institutionalized epileptics and mental defectives. Susceptibility to allergy seems to vary with type of pigmentation. It is common experience that the fair-skinned and particularly red-haired persons are more susceptible than dark-haired.

As laryngologists the factors that will interest us most are:

(1) *The Site of the Reaction*

This may be (*a*) the nose, (*b*) the sinuses, (*c*) nasopharynx, (*d*) oropharynx, (*e*) larynx and trachea, or (*f*) bronchi.

The clinical picture differs in each of these sites.

(2) *The Commonest Groups of Allergens*

Allergens are usually divided for descriptive purposes into (*a*) exogenous and (*b*) endogenous.

The exogenous are subdivided into:

(i) Inhalants: Pollen, dust, bedding, animal emanation, &c.

(ii) Ingestants: Wheat, eggs, milk, &c.

(iii) Drugs and other inorganic agents, smoke and fumes of tobacco, coal, washing powders, &c.

(iv) Physical agents: Light, heat, cold, humidity and touch.

(v) Products of bacteria, viruses, moulds, parasites.

The endogenous are subdivided into:

(i) Emotional and endocrine.

(ii) Bacteria, viruses, moulds and parasites multiplying in the body.

(iii) Altered tissue protein, exudates, transudates, inflamed and injured tissues.

During the last three years we have been undertaking a detailed investigation of cases of nasal allergy attending my Outpatient Clinic. In a group of 168 patients with nasal allergy there were 71 cases with nasal allergy alone, 59 with nasal allergy and asthma and 38 with nasal allergy and other allergies.

In these patients the relative frequency with which groups of allergens were responsible was as follows:

Inhalants	135 cases (80%)
Ingestants	59 cases (35%)
Physical agents ..	36 cases (21%)

(3) *Predisposing Factors and Triggers that Initiate the Reaction*

We also investigated the factors that might have predisposed the tissues to allergy. These factors fell into the following groups:

(i) *Heredity.*

(ii) *Infections*, including coryzas, zymotic epidemics and local infections of the nose and throat, such as rhinitis and sinusitis, pharyngitis, tonsillitis and adenoiditis .. 5[illegible]%

(iii) *Mechanical factors*, such as direct trauma by blow or surgery or indirect trauma by the pressure of mucous membrane against mucous membrane, nasal obstruction or the drying and arrest of the mucous sheet by air jets due to deviation of the nasal septum .. .. 2[illegible]%

(iv) *Psychological*, including those in which the onset followed immediately on some emotional shock .. .. 1[illegible]%

(v) *Pregnancy and menopause* .. .. [illegible]%

(vi) *Environmental and occupational*, including patients who were exposed to occupational dusts and fumes .. .. [illegible]%
or, in the case of mould allergy, those who lived in old houses .. .. 3[illegible]%

It has been suggested that mould allergies are particularly common in damp climates. The district in which I work has a high rainfall, and being near a large estuary and several rivers, usually has a high atmospheric humidity. Thus our figures of 40% compare with those of Van Leeuwen (1924) for Holland, who found 50% of asthmatics allergic to fungi. But Fraenkel (1938) in Germany, where the climate is dry, found only 16% were sensitive to fungi.

If we consider these factors it seems reasonable to assume that, given a receptive soil, as provided by a strong hereditary predisposition, the initiation of allergy is likely to follow exposure to a heavy concentration of potent allergens at a time when tissue resistance is lowered, and the surface laid open to the entrance of allergens. This depression of resistance may be general—due to chill, fatigue, emotional disturbance or general disease; or local—due to inflammation, trauma or drying of the mucous sheet. Of all the factors the most important is infection.

As experimental evidence of this a very interesting observation was made by Burky in 1934. Working with bacterial products on rabbits, he was able to show:

(i) Classical shock in the sensitized animal.

(ii) Passive transfer.

(iii) Positive reaction in the Dale uterine muscle strip.

(iv) Arthus type reaction (Arthus, 1903).

He noticed that when immunizing rabbits to a staphylococcal toxin the animal became sensitized to the culture medium broth. One of the strange features about allergy is that while clinical allergy is so common and widespread it is practically impossible to sensitize human beings or animals experimentally to any of the common allergens, except perhaps poison ivy. Burky found that he could, by using the staphylococcal toxin, sensitize rabbits to ragweed, and even to their own crystalline lens or muscle protein.

Thus through the agency of staphylococcal toxin an individual might during infection become sensitized to other allergens. Swift and Schultz (1936) have produced similar results using diphtheria and staphylococcal toxin. Also Swineford and Holman in 1949 were able to show many skin reactions in sensitized individuals using nucleoprotein and polysaccharides from 14 different bacteria, the carbohydrate fraction producing an immediate reaction and the protein a delayed one.

There are many clinical examples of infections with associated allergic skin reactions and local allergic reactions in different organs. Scarlatinal rashes and glomerulo-nephritis, rheumatic carditis and many syphilitic lesions are examples of this type.

Allergy, once established, is augmented and encouraged to spread from one shock tissue to another by repeated exposure to the allergens, and by depression of the patient's general and local resistance. The more frequent the attacks the easier it becomes to elicit them. It is often noted that single allergens may not be sufficient alone to cause a clinical reaction, but when there is simultaneous exposure to others, attacks come on. It must also be remembered that with the same allergen and the same individual the site of reaction may shift in the course of time; and that different allergens in the same patient may affect different tissues. A striking example of this is provided by the patient who during the hay season suffers from bronchial asthma and in the ragweed season from nasal allergy.

(4) *The Clinical Picture*

General Features

Acute allergy.—The clinical picture is that of an inflammation with the following five special characteristics:

(i) The excessive irritation and œdema of the reaction compared with the small amount of the allergen producing it.

(ii) The explosive nature of the onset of the symptoms on exposure to the allergen, the short latent period and the abrupt cessation of irritation and rapid recovery of the tissues on elimination of the allergen.

(iii) The absence of tissue destruction or suppuration and the watery nature of the discharge.

(iv) The eosinophilic response.

(v) The absence of pyrexia and general toxæmia.

Chronic allergy develops when acute attacks follow one another so rapidly and for such a long period of time that the tissue cells proliferate and lead to hyperplasia, while the œdema becomes fixed and leads to general thickening of the tissues and also to the development of polypi (Fig. 1).

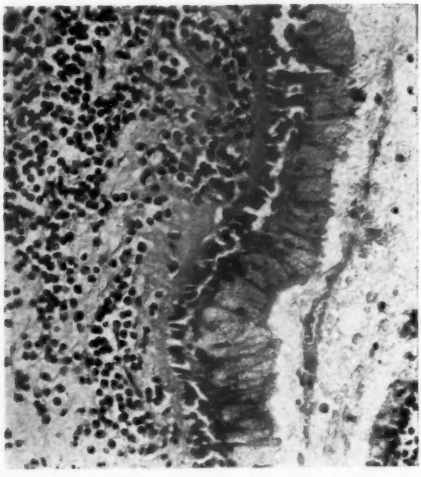


FIG. 1.—Nasal polyp showing œdema and eosinophil infiltration. H. and E. ×182.

Local Features

Acute nasal allergy is divided for clinical purposes into: (*a*) Seasonal or pollinosis, due to pollens. (*b*) Perennial, due to the remaining allergens.

The two groups may be combined. The difference is of importance in both treatment and prognosis.

In nasal allergy the patient is often sensitive to a number of allergens. The inhalants are the commonest causes in adults, but in children the food allergens, particularly wheat, eggs, milk and chocolate, are more frequently responsible. At both ages physical allergens, particularly changes in temperature, the effect of wind and the alteration of nasal reflexes as in excitement or exertion, are responsible for sudden outbreaks of allergic reaction. In a few the nose may be so hypersensitive that touching the lip is sufficient to set off a paroxysm of sneezing, while in a considerable number the lightest touch with a probe directly on the nasal mucosa causes a violent protective reflex with sneezing, lacrimation, rhinorrhœa and mucosal swelling.

During the active phase the patient suffers from paroxysms of sneezing. The mucous membrane is characteristically swollen and boggy causing obstruction of the airway and is bluish in colour due to œdema, vascular engorgement and blood stasis. The secretion is copious and watery and contains eosinophils. During the quiescent phases the appearance may be normal. When the allergens are mainly bacterial or physical agents the mucous membrane is often red in colour and eosinophils are absent from the secretion.

Chronic nasal allergy.—The characteristic features are those of permanent nasal obstruction and viscid nasal discharge with episodes of superadded acute allergic manifestations on re-exposure to the allergens. From these characteristics it is not surprising that the commonest allergens causing this type of allergy are bacteria and house dust.

Nasal sinus allergy is much less common than nasal allergy, and is nearly always the result of spread from the nose. When it does occur primarily it is usually due to foods. In many cases the swelling of the ostium leads to retention of secretion and secondary bacterial infection. In due course untreated cases of this type develop a bacterial allergy to add to the complexity of the picture. Polypi soon form and the disease beginning in one sinus gradually spreads, by obstruction and infection, to the other sinuses. In spite of the obstruction

and the gradual expansion of the nasal and sinus chambers by the pressure of the enlarging polypi there is very little pain or general malaise.

Nasopharyngeal and pharyngeal allergy are much less common than nasal allergy because of the thicker mucous membrane and the protection afforded by the nasal passages.

It is seen most commonly in children when allergy may play a part in causing excessive œdema and hyperplasia of the adenoids and tonsils. It should be suspected when diffuse lymphoid hyperplasia resists treatment and recurs repeatedly in spite of every care; bacterial allergy then usually plays a part, as well as sensitivity to inhalants and ingestants.

In adults the usual complaint is of tickling and irritation of the palate. There may be hypersensitivity to very hot, very cold or highly spiced food, which in severe cases cause coughing and choking. As with other allergies of the nose and bronchi the patient is often woken up by an attack in the early morning, or this begins on waking or on rising from bed. The triggers that initiate the reaction then are the changes of temperature and the changing of the patient's metabolism and particularly the rise in metabolism and sudden activity in the upper respiratory tract after rest.

The following is the history of such a case.

A woman aged 58 complained that for eight years she had had severe paroxysms of dry tickling cough from the throat lasting ten minutes. After consulting many doctors she was finally treated by ultraviolet light and before the course was finished she had developed also violent attacks of sneezing and rhinorrhœa. The attacks came on at any time of the day or night and she was often woken by them in the early morning. They were induced by change of temperature, a close atmosphere, tobacco smoke, laughing and eating sugar or cheese. They were relieved by hot whisky and particularly by liquorice. During the paroxysm she was unable to talk.

The only physical signs were those of definite sepsis in both small buried tonsils. Touching the tonsils immediately induced an attack. Skin tests for inhalants and ingestants were negative. She was relieved by antihistamines.

Of interest in this case was the allergization to ultraviolet light during treatment and the patient's observation of the special effect of liquorice.

Angioneurotic œdema provides another type of pharyngeal allergy, in which obstruction is the chief feature, and foods are the most frequent allergens.

Laryngeal allergy is seen in children in the form of croup. In adults it presents as paroxysms of dry cough, which may even prevent phonation, and possibly in an extreme form may cause vertigo and loss of consciousness. This is one of the causes of "laryngeal vertigo". The typical cough reaction, like that of asthma, is sometimes most severe in the early morning or following exertion or laughing. Angioneurotic œdema may also occur in the larynx and cause obstruction as it does in the pharynx. It is probable that cases of chronic hypertrophic laryngitis seen in stokers and workers in the paint industry represent localized physical and chemical allergies.

(5) *Diagnosis and Special Methods of Diagnosis*

(*a*) *The history is of special importance*, particularly if the patient is seen in a quiescent period.

(*b*) *Routine general clinical examination.*

(*c*) *Specific skin tests.*

I must confess to having been very sceptical of the value of skin tests in my earlier days. Perhaps I was biased after being consulted by a lady who informed me that while she was living in California she was submitted to 420 skin tests, and that she proved sensitive to 140 of them. With advancing experience I have learned to regard them with much greater respect, and I now consider that they often provide most valuable information. They seem to be most dependable for inhalant allergens, much less dependable for ingestants, and of very little value in bacterial allergy.

In my recent series of 168 cases of nasal allergy we obtained positive skin tests in all but 10. At the same time control tests in 128 clinically non-allergic individuals gave positive results in 24; the remainder were negative.

The interpretation of these tests is often difficult and can only be considered with the history and clinical picture. They are not sufficiently reliable for accurate quantitative assessment and the degree of allergization of the skin and of the upper respiratory tract may be different. The tests record the effect of single allergens while the clinical effect is, as we have seen, often due to the action of multiple allergens simultaneously.

(*d*) *Intranasal tests.*—The best technique of intranasal testing is that of the powder puff. Wool is wound on to a carrier and dipped in the powdered allergen. This is held to one nostril and the patient is instructed to sniff with the other nostril closed. They are of value when the skin tests are inconclusive.

(*e*) *Diet elimination tests.*

(*f*) *Examination of nasal secretion.*—We have found it best for the patient to blow secretion into a sterile cellophane handkerchief which is screwed up tightly in a screw-cap bottle for transport to the laboratory where a differential cell count is made. Hansel (1936) maintains that over 10% of eosinophils indicates allergy but since the eosinophils are only present in the active phase their absence does not exclude allergy. When the eosinophils are very numerous the secretion may resemble pus macroscopically (Fig. 2).

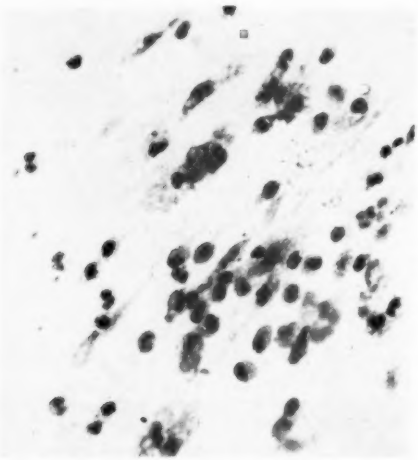


FIG. 2.—Smears of nasal secretion to show eosinophilic pus. Leishman × 390.

(*g*) *Bacteriological examination of secretion.*—Smears should be taken directly from the middle third of the nose under direct lighting and using a sterile nasal speculum to avoid contamination from the anterior third of the nose. Positive cultures indicate active infection, but failure to obtain a culture does not exclude the presence of infection.

(*h*) *Radiographs of the nasal sinuses* should be taken in all but the minor cases. The presence of allergic changes in the sinus mucous membranes are shown in the slightest degree by mottled clouding, and in the more severe degrees by definite polypoid changes or complete opacity, the last being due either to polypi or to polypi and retained allergic secretion or pus.

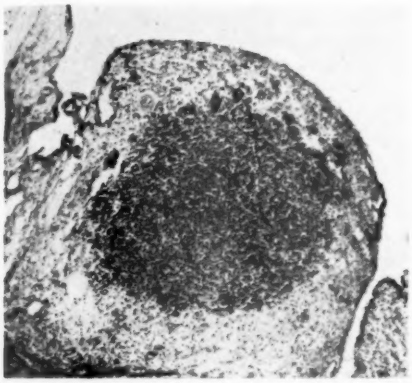


FIG. 3.—Antral mucous membrane showing eosinophil granuloma in the submucosal layer with fibroblasts in the stroma. H. and E. × 49.

(f) *Histological examination.*—In very complicated cases I have found it useful to take a biopsy specimen from the inferior turbinal with a very fine aural granulation forceps. Under local anæsthesia it is quite painless, heals completely in a day or two and causes no disability.

The relative degrees of allergic and inflammatory reaction are well seen and an assessment of the degree of chronic change can also be made.

In inhalant and ingestant allergies eosinophil infiltration will be seen in the active phase, whereas in infective and bacterial and physical allergies eosinophils are absent.

(6) *Treatment*

Methods of treatment fall into the following groups:

(1) Elimination of the predisposing factors. (2) Avoidance of the allergens responsible. (3) General treatment with vitamins, acids, calcium, &c. (4) Specific hyposensitization, including the use of bacterial vaccines. (5) Palliative treatment with: (*a*) Antihistamines. (*b*) Hormone therapy. (*c*) Sympathetic stimulants and parasympathetic depressants. (*d*) Glycyrrhetinic acid. (6) Ionization. (7) Cauterization. (8) Psychological.

General Considerations in Treatment

It is important to remember above all that we are treating a patient and not only his disease. In selecting treatment care must be taken that the cure does not prove more unpleasant than the disease. It is by no means uncommon for minor allergy to subside spontaneously but it is important that severe allergy should be checked by all reasonable means. The longer it is allowed to continue the more severe it is likely to become and the greater the risk of spread to other tissues, the development of multiple allergies and of superadded infection. Short attacks of up to half an hour do not need treatment.

In seasonal allergy if the seasons are short and the attacks not severe it is justifiable to rely on antihistamines, hormone therapy and the other groups of drugs.

In perennial allergy we should eliminate predisposing factors as far as possible and build up the general condition to reduce the sensitivity.

In these cases the treatment of infection is of the greatest importance. Then the allergens should be identified by the history and specific testing and elimination diets and cultures. The patient is given instructions how to avoid, as far as possible, contact with them. This may be all that is necessary, but if it does not give sufficient relief specific hyposensitizing injections should be used. In our series improvement was obtained in 50% of cases by these measures. The most successful results in hyposensitization are achieved in seasonal pollinosis. By annual pre-seasonal courses of inoculation in increasing doses 70–80% of sufferers can be rendered comfortable. Treatment should be continued for at least two years after complete freedom.

Treatment of the predisposing factors.—Apart from heredity the two main predisposing factors to upper respiratory allergy are obstruction and infection. I am convinced now that because of their hypersensitive nervous state, allergic patients suffer much greater discomfort from moderate degrees of deviation of the septum and of sinusitis than the non-allergic and one's standards of indications for operations should be adjusted accordingly. This does not mean that drastic sinus surgery should be undertaken if a moderately severe sinusitis is discovered in an allergic patient.

If some infection persists in spite of the most careful treatment, then an autogenous vaccine should be given. Autogenous vaccines are often of great therapeutic value in the infected allergic patient provided that all foci have free drainage: they should not be used for chronic sinusitis without adequate drainage.

Polypi deserve special consideration. Their presence is almost certainly an indication of allergy. The small sessile polypi which develop on the middle turbinal and also in the accessory sinuses will shrink in many cases with adequate treatment of the allergic factor. But if those in the nose do not respond quickly they should be removed to restore a complete nasal airway and to allow ciliary action and recovery of the protective mucous sheet. Simple allergic polypi in the sinuses do not require surgical treatment unless they become subject to recurrent attacks of inflammation or block the sinus ostium.

Chronic sinusitis with allergy and polypi in the sinuses and in the nose should be treated by operation. The polypi should be removed from the sinuses as well as the nose and adequate drainage established. It is of the greatest importance to make certain that no foci of infection remain. As many of these patients have a bacterial allergy they continue to suffer severely if even a very minor focus is overlooked.

We have found operations necessary in 15% of our cases and have obtained relief in 80% of cases treated by operative and specific allergic treatment.

(7) *Palliative Treatment*

General considerations.—Antihistamines, hormones, sympathetic stimulating and parasympathetic depressant drugs are useful to tide a patient over a severe exacerbation, and also for treatment of short seasonal allergies, but they are not really curative and the symptoms recur when the drug is stopped. In some instances, however, prevention of reactions by such means for a matter of months or years has been sufficient to allow the shock tissues to recover and the patient's symptoms have not recurred on ceasing the drugs. But such a fortunate result is rare.

Antihistamines.—There is now a long list of antihistamine drugs which differ in quite minor degrees from one another. The duration of action of most antihistamines is only three to four hours, but Phenergan will last up to twenty-four hours. Unfortunately most of these drugs also cause drowsiness of variable degree when given systemically, but they are also valuable when used locally.

In order to counteract the drowsiness antihistamines can be combined with an analeptic, as in Plimasin, which contains Methyl Phenidylacetate 5 mg. and Pyribenzamine 25 mg. The former is intermediate in action between caffeine and amphetamine

In severe allergy the dosage required is so large that the undesirable side effects are too great before the patient has reached the necessary concentration to block all the histamine.

For some years there was a vogue for desensitization with histamine, but it is now very rarely employed.

DRUGS ACTING ON THE PERIPHERAL NERVES

Sympathetic Stimulants	*Parasympathetic Depressants*
Adrenaline	Belladonna
Ephedrine	Atropine
Phenylephrine and other synthetic drugs	Hyoscyamus
Ergotamine	Stramonium
Caffeine	
Aminophylline	

Local anæsthetics.—Cocaine, Novocain, and other local anæsthetics, depress local sensitivity and suppress allergic reactions.

Sympathetic stimulants.—Of the proprietary preparations, Fenox, which contains the two vasoconstrictors phenylephrine hydrochloride 0·25% and naphazoline nitrate 0·025%, is the most powerful and long-acting, but its indiscriminate use has had a remarkable habit-forming effect. I have seen a dozen or more patients who, having begun to use these drugs locally as drops, have continued to apply them every three or four hours for months and in some cases for years. Several of these patients have even woken up once or twice every night for further application. As the effect passes off the nasal obstruction becomes complete and the patient is frantic until relieved by a further application. The nasal reflexes are paralysed and the constrictive effect of other drugs diminished (Fig. 4).

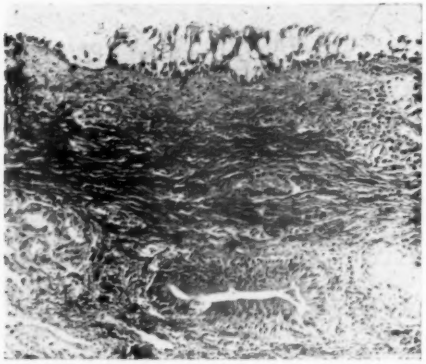


FIG. 4.—Nasal mucosa from a case of Fenox addiction showing an unusual degree of fibrosis in the upper part of the submucosa replacing the basement membrane. There is intense vascular engorgement, patchy denuded epithelium and the remainder shows mucous distension. Eosinophils are absent. Aniline blue trichrome ×85.

If the Fenox is discontinued the reaction subsides in the course of several days but in order to overcome the habit the patient may have to be admitted to hospital and assisted with sedatives and treatment of the allergy and the nasal airway restored by correction of abnormalities.

Hormones.—The hormones cortisone and hydrocortisone may be used generally or locally in a spray or snuff, these drugs are powerful suppressors of the allergic and inflammatory response to infection. They cause a rapid disintegration of eosinophil cells and lymphocytes in the blood and release many antibodies. They have a number of undesirable side-effects, chief amongst which are salt and fluid retention leading to œdema and moon face.

By systemic treatment good results in nasal allergy were reported by Stewart (1953) and more recently Herxheimer and McAllen (1956) have reported success using a hydrocortisone snuff for hay fever.

Recently two synthetic analogues of cortisone and hydrocortisone, prednisone and prednisolone have been introduced with four or five times the potency of the previous drugs. They are also much less likely to induce undesirable side reactions and should prove a useful addition to our choice of treatment. Their effect on allergic œdema is so great that systemic treatment with these drugs is reported to have caused even fully-developed polypi to disappear.

More recently still a new anti-inflammatory agent has been described in extract of liquorice. The active principle is glycyrrhetinic acid and is used locally. Its molecular structure bears a close resemblance to that of hydrocortisone and there are preliminary reports of its anti-inflammatory action in skin diseases (Colin-Jones, 1956). Liquorice has been used as a constituent of sedative throat lozenges for many years.

Cauterization and ionization.—It is unfortunately true that the preceding treatments do not give relief in all cases, and then zinc ionization and light cauterization (Francis, 1932) are of some value. Linear cauterization is also the best and safest method of reducing the thickness of the mucous membrane in chronic allergy. None of these methods should be employed until the best result has been achieved by the other measures.

Conclusion

Finally, although the understanding of the essential nature of allergy still evades us, we are fortunate in having a wide choice of different methods of treatment. With the rapid advance in biochemistry and biophysics the day may not be far distant when a specific curative measure will be found to relieve the millions of sufferers from this miserable complaint. In the meantime there are already valuable methods of treatment that can give very adequate relief to the majority of patients.

But to succeed, our investigation must be thoroughly performed and treatment meticulously carried out with the closest collaboration between the allergist, pathologist and laryngologist.

I am greatly indebted to Dr. H. Saphier, who has undertaken the detailed investigation of many of my patients in the allergy research clinic at the Bristol General Hospital. I wish to thank Dr. A. L. Taylor for his help and advice on the pathological problems, and Dr. E. Price for the preparation of the photomicrographs.

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Mr. F. C. W. Capps said that in tackling so difficult a problem, the President had given them an authoritative survey for reference.

Mr. C. Gill-Carey said that lack of accurate means of assessing the results of treatment had been his main problem. In a high percentage, both the nasal examination and the statements of patients were indeterminate. Nasal biopsy, carried out in a number of cases, had also been unreliable as a means of assessment.

Mr. H. V. Forster said that many years ago he had read that on this side of the Atlantic ragweed pollen might appear as an autumn irritant. The pollen was said to disperse over great distances and even to high altitudes where observers had collected it using the aeroplane.

Had the President noticed in his overall clinical assessment of the allergic adult patient a rather high quality of the individual teeth apart from their regularity?

When examining a child, who after all rarely spoke for himself, it was a matter of the highest priority for the laryngologist to be on the look-out for signs of allergic nasal catarrh. It was to be separated from the adenoid problem where one might see a quiescent nose with adequate passages striving hopelessly to pass air across a wall of post-nasal adenoid. The intrinsically dirty nose was often a state independent of adenoids.

A picture less hopeful was that of established purulent sinusitis with a history of infantile bronchiectasis to remind the laryngologist of his duty to co-operate with his physician colleague not least, when he had discovered a case of typical nasal allergy with its permanently wet nose and pale waterlogged inferior turbinates.

He would agree with the President that the surgical treatment of this body, which may have been harshly treated in olden days, should be most conservative. It was part of a superb air-conditioning mechanism and yet would often respond gratefully to linear cautery with the galvanic point, a minor operation done so conveniently under local surface anæsthesia in the adult but unfortunately calling for a general anæsthetic in the normally apprehensive child.

Mr. Philip Jory said that in a number of cases an allergic upset preceded the onset of the common cold. For some years he had been prone to develop a severe cold after long out-patient sessions, but had found that if he took an antihistaminic as soon as he felt the first symptoms he could almost always prevent the cold from developing. However, once the cold had become established the anti-histaminic appeared to have no curative effect.

Mr. W. A. Mill mentioned that wines and sherries not uncommonly gave rise to allergic rhinitis and he had met a patient in whom whisky had the same effect.

Mr. W. O. Lodge asked if the President, on looking through his case-books, had noticed whether most young males in particular grew out of their allergies or died at an early age from bronchiectasis and whether any significant proportion of patients with recurrent nasal polypi developed frontal sinusitis in adult life or—eventually—carcinoma.

Mr. R. D. Owen asked whether, in cases who came complaining of sneezing and wheezing and had real polypi, *conservative* treatment was found satisfactory. If it was decided to operate, was the operation conservative, dealing with just the polyposis, or was it a more radical operation in the form of transantral ethmoidectomy?

The President, in reply to Mr. Mill, said that he had had several patients who were allergic to alcoholic liquors, and that the commonest of all was sherry.

In reply to Mr. Lodge, he agreed that the young asthmatic presented a difficult problem, but that if nasal function was restored, the infective foci eliminated and the allergic factors carefully treated, a considerable number could be satisfactorily relieved of their symptoms. He commented that carcinomatous changes in nasal polypi were very rare.

In reply to Mr. Owen, when nasal polypi were associated with polypoid changes in the sinuses and complicated by chronic or recurrent infection, he advised opening the affected sinus and removing the polypi and thickened mucous membrane.

In reply to Mr. Forster, the President said that ragweed pollen was probably the commonest cause of pollinosis in the United States. Its season was the autumn, but in his experience it was rare in this country. He had not noted a particular quality of individual teeth among allergic patients.

Section of Orthopædics

President—E. STANLEY EVANS, C.B.E., F.R.C.S.

[*May* 7, 1957]

SYMPOSIUM: THE USE OF METAL IN BONE SURGERY

Mr. G. K. McKee (Norwich):

History.—The story of the use of metal in bone surgery has not been a particularly happy one. Pioneers such as Lane and Lambotte were striving after perfect reduction and secure fixation in the treatment of fractures, but their efforts were spoilt by the use of unsuitable metal. The use of metal in bone surgery presents two problems:

A. Corrosion or the reaction of the metal in the body tissues.

B. The indications for the use of metal in the treatment of bony injuries and diseases.

Both these problems are closely related because the indications for the use of metal will increase as the corrosion rate decreases, i.e. as more suitable metals or metallic alloys are found.

It is impossible to deal with either completely, so I propose to limit my comments to a report on some corrosion tests carried out for me by Mr. D. H. McCracken of the Engineering Department of the City of Norwich, and to some of my own personal experiences in the use of metal in bone surgery.

A. Corrosion Tests on Metals Used for Internal Fixation

It is assumed that the corrosion of metals in the body is largely due to electro-chemical action. The tests were therefore designed to compare the relative rates of electro-chemical attack on two types of stainless steel and on the non-ferrous alloy Vitallium.

If two different metals are in contact and are immersed in an electrolyte such as a body fluid, one metal will become electrically positive relative to the other. Current will flow from metal to metal through the point of contact from the positive metal to the negative metal. The circuit is completed by the current flowing through the electrolyte, from negative metal to positive metal. Thus an electrolytic cell is formed in which the negative metal is the anode and the positive metal is the cathode.

If the electrolyte contains Cl ions these will migrate to the anodic metal and give rise to chemical attack. The result is usually oxidation of the attacked metal. Some metals, such as those under consideration here, tend to form oxide films which have a high resistance to penetration by ions. Should a perfect oxide film be established this will suppress all further attack and the metal is said to have become "passive". The metal which is "cathodic" experiences no attack under these simple basic conditions.

If two identical metals are used to form a cell then no electrical potential difference is created between them, no current flows and there is no attack. In practice it is virtually impossible to produce metal components of identical material. Plates and screws for example will be produced from different metal stocks and although of the same nominal composition there will inevitably be some slight differences. Surface working during machining operations will itself create some degree of electrical potential. The creation of a passive oxide film on the anodic metal must therefore be the main barrier against corrosion.

It has been established that the presence of molybdenum in an alloy is an aid to the establishment of a barrier film of oxide and recommendations have been made that if stainless steel is to be used for internal fixation it should contain some 2½% to 3½% molybdenum.

Production of screws is simplified if one of the "free-cutting" stainless steels such as Firth's EMS is used. This contains only 0·3% molybdenum. There is an obvious danger of strong corrosive attack if EMS screws are used in conjunction with molybdenum steel plates.

Materials Tested

Firth's FMB	C 0·12,	Si 0·2,	Mn 2·0,	Ni 8/12,	
	Cr 17/20,	Mo 2·5/3·5.			
Firth's EMS	C 0·12,	Si 0·6,	Mn 1·2,	Cr 18,	Ni 10,
	Mo 0·3,	Ti 0·6,	Zr 0·25.		
Vitallium	Co 65,	Cr 30,	Mo 5.		

Cells were set up with the metals as electrodes in various combinations in an electrolyte, and the strength and duration of the currents produced were measured. From the experiments the following conclusions can be drawn:

Vitallium appears to be quite free from corrosion. Presumably a completely passive film is built up very quickly and the film remains stable.

With the various stainless steels, corrosion must be expected. The worst conditions are when two different steels are used in conjunction. Plates and screws made of the same material will corrode, even when both contain 2½% to 3½% molybdenum. The screw is anodic and, therefore, suffers greater attack than the plate. Vitallium screws used with FMB stainless steel plate are not attacked; the plate being anodic does show some evidence of corrosion but not more than when used with a stainless steel screw of the same composition.

As a result of these experiments I have been using Vitallium screws and stainless steel plates ever since 1942 and have never seen any reaction around the screws, although there has often been considerable corrosion around the plate. The only difficulty with regard to the use of Vitallium screws is that, after being in for some years, they tend to bond on to the bone and may be extremely difficult to remove. In many instances, however, where screws of stainless steel have been used with a nail and plate of the same composition, FMB, there has been considerable reaction around where the screws and plate are in contact and the screws become loose in time. The experience in the use of these metals in the body over a period of fifteen years or so has confirmed the conclusions arrived at by Mr. D. H. McCracken.

B. Indications for the Use of Metal in Bone Surgery

Stainless steel of the variety known as FMB appears in practice to be quite satisfactory where a temporary fixation is required, e.g. in cases of fractures and arthrodesis operations, but where a permanent metallic insert is required to remain tightly bonded on to the bone as a functioning prosthesis, for example in the various types of arthroplasties, then undoubtedly chromium cobalt alloy is not only the most satisfactory, but in my opinion is at present the only material to use.

A lag-screw arthrodesis of the hip (McKee, 1957) is a good example of the use of stainless steel for fixation and compression; fixation was sufficient to avoid the use of plaster in 76% of the cases. The nail and plate for pertrochanteric fractures and the Küntscher nail for fractures of the femoral shaft are further examples of the use of stainless steel as a means of temporary fixation.

Many years ago, soon after cup arthroplasties had become popular in 1939, I designed an *artificial hip-joint*, but it was not until a lag screw had been used for an arthrodesis of the hip that it was realized that the most satisfactory way of securing an adequate hold on the ilium was by a large coarse-threaded screw. In fact this type of screw obtains such a firm grip that the idea to develop a ball and socket joint at the hip level, so as to retain a certain amount of mobility, was a fairly obvious one (Fig. 1). In the first series the lower end of the joint was fixed by a plate to the lateral aspect of the femoral shaft in the same way as in the lag-screw arthrodesis. Three artificial hip-joints were made up in this way (Fig. 2), and they all proved very satisfactory to start with, but in each case the stainless steel screws eventually loosened or the neck of the stainless steel plate fractured with resultant failure.

These 3 cases were failures because of the use of unsuitable metal, but they convinced me that the artificial hip-joint offered unique advantages as a form of arthroplasty, especially in cases where the acetabulum was corroded. A design for the manufacture of an artificial hip-joint entirely in chromium cobalt alloy (Vinertia) was developed, using a larger ball, and the suggestion of Mr. John Bunyan to use a tulip cup with three petals to grip the ball eliminated the complicated screw rim which had been previously used (Fig. 3).

This design has been used in 5 cases since May 1956, and the acetabular portion has been found to be most satisfactory; the design of the femoral portion has, however, had to be altered. First of all, a femoral blade, like those used on Thompson's prosthesis was tried, but as the first cases were salvage operations for failed acrylic prosthesis, the grip in the hollowed-out neck of the femur was not felt to be adequate, and eventually a broad coarse screw was used, long enough to traverse the whole neck, and engage the thick strong lateral femoral cortex; this gives an exceptionally secure fixation even where the neck of the femur is just a shell (Figs. 3 and 4). It is too early to make any extravagant claims, but with the use of Vinertia there is every reason to expect that it will last in the body for many years.

The first few cases were fairly desperate ones where pain was a prominent symptom; the roof of the acetabulum having gradually eroded away and the acrylic prosthesis being broken or loose. The replacement by an artificial hip-joint seemed to offer a better answer to this problem than any other form of arthroplasty because it reconstructed the acetabulum and the results so far show that these patients have steadily improved month by month as regards losing their pain and increasing their activities. The fixation obtained by the latest design has been so satisfactory that its application has been extended to bilateral cases in old people, and to unilateral cases if arthritic changes are present in the lumbar spine.

The follow-up of these cases so far indicates that the artificial hip-joint offers a functional result comparable with arthrodesis, but without the disadvantages of a completely fixed hip. The range of movement obtained is not as full as in a normal joint, but it does enable the old patient to sit down in comfort. Before this type of operation is carried out, symptom

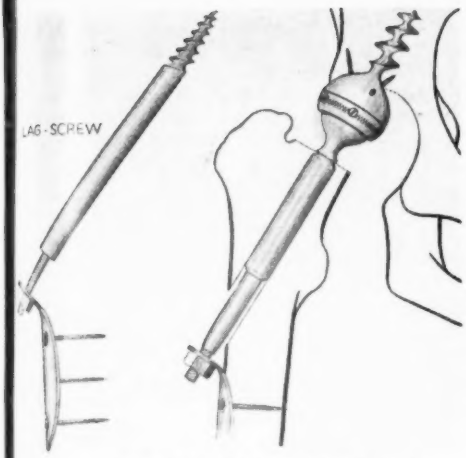


FIG. 1.—The first artificial hip-joint, derived from a lag-screw.



FIG. 2.

FIG. 2.—X-ray taken over two years after the insertion of the artificial hip-joint, showing recalcification as a result of active use and weight-bearing following operation.

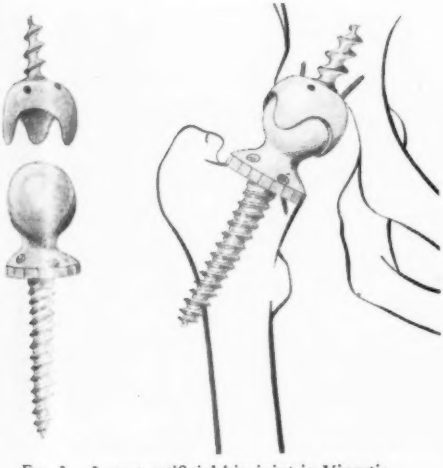


FIG. 3.—Latest artificial hip-joint in Vinertia.



FIG. 4.

FIG. 4.—X-ray showing the latest model (Fig. 3) inserted.

must be of a considerable degree of severity, and if in doubt the patient must be kept under observation for several months or even a year or two before operation.

The artificial hip-joint does, however, help to solve the problem of the failed acrylic prosthesis especially where the acetabulum has become eroded.

Reference.—McKee, G. K. (1957) *J. Bone Jt. Surg.* **39B.** In press.

Mr. John Charnley (Manchester): *The Reaction of Bone to Metal*

I wish to consider the mechanical factors, that is to say simple mechanical stresses and strains, which may be concerned in the loosening of metallic fixation in bone.

There are two different aspects to be considered: (1) the short-term problem, seen in the internal fixation of fractures, where successful union of the fracture renders the internal splint functionless, and (2) the long-term problem, seen in prosthetic replacements, where the metallic implant is expected permanently to bond itself to bone and share in the transmission of stress and strain without loosening.

I shall confine my remarks to the mechanical causes of the loosening of metallic fixation because I do not believe that electro-chemical reactions which can occur between metals of slightly dissimilar composition present anything more than a subsidiary problem. While it is obvious that all forms of corrosion must be eliminated in prostheses which are to remain permanently in the body, the problem is quite different in the short-term function of internal fixation in the union of fractures. Electro-chemical reactions are situated at a considerable distance from the fracture site, and I think it would be more profitable to re-study the whole problem of internal fixation in relation to the biology of fracture union rather than transfer blame to small technical defects in modern apparatus. We must not forget that Arbuthnot Lane established the internal fixation of fractures even though he used plates of reactive steel held by brass screws, a combination infinitely worse than any we use at the present moment.

When we consider the mechanical factors responsible for the loosening of metallic fixation, I suggest that the following features are worthy of special consideration:

(1) *The reaction of bone to metal in the absence of transmitted stress.*—It is no uncommon experience to find it impossible to extract screws from a plated fracture if there has been an interval of months or years after union has taken place. One explanation of this difficulty is that new bone grows into the "flutes" of the self-tapping end and so locks the screw against rotation, but this small amount of new bone would present no great resistance to shearing if the rest of the screw were free to turn in the bone. Difficulty in extracting stainless steel screws is even harder to explain than in cobalt chromium alloy screws, because the latter have a matt finish and one can imagine that the encroachment of new bone on such a rough surface would produce much greater frictional resistance than would be possible by the encroachment of new bone on to the highly polished thread presented by a stainless steel screw.

It seems reasonable to accept as a fact that, in the absence of transmitted stress following the union of a fracture, living bone can sometimes grip the polished surface of a non-toxic metal with a greater force than at the time of its insertion. We can therefore deduce that there is no fundamental antagonism between a relatively inert metallic surface and living bone in contact with it, and therefore that any resorption of the bone in contact with such a metallic surface is most likely to be the result of transmitted mechanical stress.

(2) *The reaction of bone to metal, with transmitted stress, in the presence of slight motion between metal and bone.*—If, as a result of technical difficulties, a metallic internal fixation is slightly loose at the end of an operation, it will never spontaneously tighten; it will, in fact, continuously and progressively become looser and the result will almost invariably be a failure.

It is difficult to be sure whether the progressive loosening of unsound mechanical fixation is the result of simple mechanical friction between the metal and the bone, or whether it is a biological process of resorption; it is probably both. A common example of this type of loosening is seen when a 4 mm. Steinmann nail is inserted through the tibial tubercle for the treatment of a fractured shaft of femur by traction. At the time of insertion this nail may be quite tight in the bone, but only too often the stirrup which is attached to the nail has a defective swivelling mechanism which prevents the stirrup turning freely on the nail without transmitting a torque to the nail and so loosening it in the bone. The same argument is against using the Kirschner wire for skeletal traction. Progressive loosening occurs even more quickly than with the Steinmann nail also because of the much higher loading, in terms of pounds to the square inch.

Motion between metal and bone and the tendency to induce mild bacterial infection.—When metal is moving against a bone surface there is always a tendency for bacterial infection to supervene, which introduces an additional cause for loosening of the metal. In the case of a Steinmann nail in the tibial tubercle the tract of infection through the skin is obvious.

But much less obvious is the spontaneous appearance of infection in cases of internal fixation where no communication with the skin exists. Hey Groves (1921), in experiments on the plating of fractures in cats, observed that when metallic fixation was inadequate, his experiments often became infected spontaneously. When, however, he used a long plate, and thereby obtained effective internal fixation, his experiments healed without infection. He decided that short plates, permitting a certain amount of motion between metal and bone, caused a collection of serous fluid at the operation site which later attracted bacterial infection.

I believe that this observation can be transferred to the surgery of the human subject. The size of the metallic implant is not related to the tendency to become infected; it is safer to have a bulky metallic fixation which is mechanically effective than a small implant which is inefficient. This is one reason why I believe that implants used in arthroplasty will always have a significant post-operative infection rate in comparison with soundly conceived procedures designed to achieve arthrodesis, because in the latter movement between metal and bone is avoided.

(3) *The reaction of bone to metal, with transmitted stress, in the absence of motion between bone and metal.*—It is an elementary engineering axiom that stress cannot exist without strain; i.e. if a force is applied to a structure the latter will be deflected or distorted according to the magnitude of the force and the elasticity of the structure. The essential feature is that, up to a certain point, during the application of stress to bone through a metallic fixation a molecular distortion of the bone can take place without any movement occurring between the surface of the metal and the bone itself. It is obvious therefore that stress can be applied to bone only up to certain limits of elasticity; beyond this point, crushing of the bone will occur and an infinitely small degree of mechanical loosening of the fixation will result; thereafter a train of events will follow, causing progressive loosening.

Where stress is applied to bone in *constantly the same direction*, without motion between metal and bone, living bone can frequently resist the action of powerful mechanical forces for several months. My observations are contrary to the accepted idea that living bone will melt away when a metallic object is pressed against it, just as a wire will cut through a block of ice. In compression arthrodesis of the knee I invariably apply a force exceeding 100 lb., yet it is a common experience to find that one, or both, of the nails may still offer resistance to extraction four weeks later. Calculations show that the load on the transfixed cortex exceeds 1,500 lb. per sq. in., and it is astonishing, but true, that after four weeks under this force such a nail often can still be tight in the bone.



FIG. 1.

Fig. 1 shows how differently cortical bone and cancellous bone react under high mechanical pressure. In an ankle-joint fused by compression the tracks of the nails through which the compression force was originally inserted are still clearly visible in the X-ray. It will be observed that the hole in the dense cortical bone of the lower end of the tibia shows no reaction whatsoever; the hole is perfectly circular and shows no ovality, as one might expect if some absorption took place. The nail extracted from this site was quite firm four weeks after the operation. This lack of reaction strongly suggests that the cortical bone at this point of the tibia is extremely inert. On the other hand, the track of the distal nail through the cancellous bone of the talus shows that there has been a considerable sclerosing reaction under the influence of the pressure. It will be observed that the response of the cancellous bone is *not an osteoclastic response;* it is on the contrary the reaction of sclerosis resisting pressure.

Observations on spring-loaded screws.—I have had considerable experience with the application of spring-loaded pressure to cancellous bone, using screws with large-diameter helical threads. If the screw is protected from angulating strains and a pure longitudinal pull is applied, the spring will retain its pressure for even as long as one year before the spring opens to its full length. It is too early at the moment to make any positive calculation from these observations, but it is my impression based on calculations of the total surface area of the helical threads that, provided the pressure is constantly in one direction and no movement takes place between metal and bone, cancellous bone can resist a pressure of probably more than 25, and something less than 50 lb./sq. in. for longer

than six months before finally yielding to the pull of the spring. When the screw is first inserted the traction force will be exerted principally on the first one or two helices and will thus shield the remaining helices from the full force of the spring. If this force is too great for the mechanical strength of the bone some collapse will occur until all the helices receive approximately the same thrust.

I take this opportunity of making the suggestion that experiments with spring-loaded screws applied to suitable animals would yield fundamental information on the reaction of living cancellous bone to pressure in the absence of movement. This could be done in the absence of fractures which in the human subject always complicate the interpretation of extrusion of the screw under spring-loading.

Osteoclasis and remodelling.—The reaction of bone to the stress applied to it through a metallic fixation depends on the duration of the stress. Three phases of duration can be distinguished. The earliest phase is that of simple mechanical loosening, caused by forces too great for the strength of the bone, or by forces acting in irregular directions which the fixation may not be designed to resist. This type of mechanical loosening will occur within minutes, hours, or days of the operation. If the force acts continuously in one direction, the second phase, I believe, is an osteogenic reaction designed to resist the applied stress. Cortical bone shows very little osteogenic reaction, but cancellous bone reacts vigorously. This osteogenic phase I believe lasts from one to two months. Beyond this time the third phase commences, which is the process of "remodelling". Here a balanced process of osteogenesis and osteoclasis is in action simultaneously with the object of neutralizing the applied stress. This phase lasts very many months and it is the mechanism underlying Wolff's law of the adaptation of bone architecture to function. If a spring-loaded compression screw is applied to bone this final phase (remodelling) will permit the screw slowly to extrude until all spring pressure is abolished and equilibrium is again attained. It is to be clearly understood that in this process the cancellous bone engaging the screw moves with the screw—a process quite different from the mechanical shearing of bone under excessive force.

Conclusions

The short-term problem.—Healthy cortical bone is remarkably inert during the first four weeks and can resist pressure between 1,000 and 2,000 lb./sq. in. without mechanical collapse or biological resorption. This resistance is only possible if no friction occurs between the metal and the bone.

Close texture cancellous bone can resist pressure of over 25 lb./sq. in. during the first four weeks and this resistance is accompanied by a vigorous osteogenic response. Even more than cortical bone, cancellous bone is only able to resist pressure in a constant direction and in the absence of friction.

The long-term problem.—After the initial period of one or two months the reaction of bone to an implant is totally directed to neutralizing local mechanical pressures by the process of "remodelling". Just how small is the minimum pressure needed to start this process of remodelling is unknown; it is probably exceedingly small because it is well known that even cortical bone will remodel under the gentle pressure of a ganglion if the latter presses against it for several years. It would therefore seem unlikely that a permanent metallic prosthesis, intended to carry the weight of the body, could ever be constructed with a method of attachment to the bone designed to diffuse the load over a large surface area such that the pressure would be reduced below that which would initiate remodelling. The problem is rendered all the more impossible when one realizes that any bone-to-metal bond would be exposed to a multitude of stress reversals in a variety of unpredictable directions.

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Mr. J. H. Hicks (Birmingham): *The Relationship between Metal and Infection*

The use of metal in orthopædic surgery is frequently criticized. Some of the criticisms are justified: others are not. One that requires careful scrutiny is the suggestion that metal causes infection.

There is no question that corroding metal has often caused inflammation, particularly in the early days of its use. I am careful to use the word "inflammation" because I believe a mistake has been to assume that inflammation signifies infection. Inflammation can be caused in other ways than by infection, however; it can be caused by mechanical irritation and by toxic chemicals. I suggest that, in fracture surgery at least, infection has in fact never been a common cause of inflammation and that often it has been assumed guilty when the real cause has been overlooked.

The toxic chemicals referred to are the products of corrosion of metal, namely, compounds of iron, chromium, nickel, molybdenum or manganese. At least two of these

are known for their poisonous properties in other spheres. Our experience at the Birmingham Accident Hospital of about one hundred cases in the outbreak of 1950–54 described elsewhere (Cuter and Hicks, 1956) was (i) that corrosion could give rise to inflammation in the absence of infection (Hicks, 1958); (ii) that corrosion enabled organisms, both pathogenic and non-pathogenic, sometimes to persist harmlessly in wounds long after they would ordinarily have disappeared; and (iii) that only in a small proportion of cases may corrosion have encouraged secondary infection.

We also realized that the inflammation caused by corrosion, or by corrosion with secondary infection, was indistinguishable, except by histological and sometimes by bacteriological examination, from the inflammation caused by pure infection. Fig. 1, showing a typical corrosion reaction, illustrates the impossibility of distinguishing clinically.

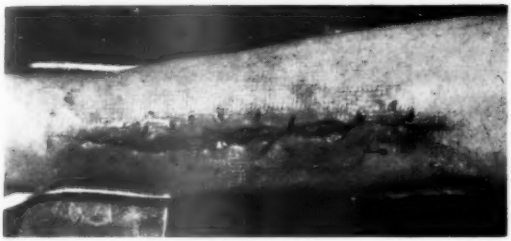


FIG. 1.

In this particular case a few staphylococci were present but in such small numbers as to make it probable that they were not pathogenic but secondary invaders. (No antibiotic had been given.) In some of our other cases, when there had been no opportunity for secondary infection, no organisms at all could be found. Naked-eye examination of the tissues was also misleading for the metal was surrounded by what appeared to be typical septic granulation tissue. Only on histological examination were differences recognized. In other cases corrosion presented as a collection of brown fluid which from its naked-eye appearance was called an infected hæmatoma. Again culture revealed that some contained no pathogenic organisms and that a few contained no organisms at all.

The distinction between the inflammation due to toxic chemicals and the inflammation due to bacterial infection is important if treatment is to be correct. The remedy for corrosion is to remove the metal together with its corrosion products, and the remedy for infection is equally specific. Similarly in prevention, it would be quite useless to tighten up aseptic regime in theatre if the real cause for the inflammation were unsuitable metal. This, I suggest, is what we actually have been doing.

Stainless Steels in Surgery

Most of the trouble in surgery has come from the use of unsuitable stainless steels. Only ordinary steel and vanadium steel were used in England for the manufacture of plates

TABLE I.—STEELS USED IN SURGERY. IN CHRONOLOGICAL ORDER

Not a stainless steel	**Vanadium steel**	Ordinary steel plus 0·1% vanadium
Stainless steels	**Chrome steel**	(Approx.) 13% chromium, no nickel
	18/8 (syn. F.S.L.)	(Approx.) 18% chromium, 8% nickel
	S.Mo. (syns. FMB, molybdenum steel) ..	As above plus 3% molybdenum
	EMS	As 18/8 plus 1·6% manganese

Corrodible steels are printed in **heavy type.**
Non-corrodible steels are printed in ordinary type.

(Note that in the conditions obtaining in the body the term "stainless" is no guarantee of freedom from corrosion.)

and screws until about 1935. These metals are now known to have a high incidence—perhaps 100%— of gross corrosion. The change-over to 18/8 stainless steel for plates and screws was not complete until 1938. For Smith-Petersen type nails during these years chrome steel was used and this continued, alternatively with 18/8, until 1941. Thus, from 1935 to 1941 two different steels were being sold under the name "stainless", one (the chrome steel) having a high rate of severe corrosion, and the other (the 18/8 or so-called "non-toxic") being relatively safe. The post-war years have been marred by EMS (Cuter and Hicks, 1956). This was a stainless steel with a corrosion rate of up to 40% introduced for certain screws unintentionally in 1950 and sold under the label of "non-toxic" over a four-year period. There has not been any long unbroken period, therefore, during which exclusively safe metal has been sold in this country.

All these changes have been slow to reach the patient and, what is worse, they have been incomplete. Steels from every period covered by this survey have been found in the theatre

stocks of some hospitals. Chrome steel and vanadium steel do not even require the stimulus of a dissimilar metal to start corroding. Inflammatory complications may therefore still arise from the use of unsuitable metals, and if the surgeon is unaware of the danger he will naturally conclude that his wounds are becoming infected.

Next I want to show how, as a result, the mistaken idea has been built up that bone is peculiarly susceptible to infection.

Lane was one of the first to assume that the inflammatory reaction he was seeing after plating was due to infection. The no-touch technique was his attempt to carry oligosepsis to an extreme. Surgeons failed to consider the possibility that the steady undercurrent of inflamed wounds might be due to some entirely different cause. A paper by Dahl-Innersen in 1928 represents the uncritical attitude that has persisted ever since: he accepts that infection was the cause of the trouble without ever considering the bacteriology. The signs and symptoms of osteitis which he lists include all the effects that we now know to be produced by pure corrosion, by pure infection and by the two combined.

I suggest that for the first forty or fifty years of this century corrosion occurred with great regularity, that it was always mistaken for sepsis and that the whole tradition that bone is particularly susceptible to infection is based upon a fallacy.

It might be argued that even if this is correct it does not matter: unnecessarily elaborate precautions will have been taken for the past forty years but apart from the extra work involved no harm has been done. This is not true, however. A firm teaching based upon the fear of infection has grown up banning internal fixation as a routine treatment for compound fractures. But if any group of fractures is likely to benefit by internal fixation it is the severest group, which will contain most of the compound fractures. Thus the present teaching denies to these fractures a treatment most likely to be useful.

At the Accident Hospital, even before the recent outbreak of corrosion was dealt with, we were convinced that internal fixation had a large place in the treatment of fractures. Of the shaft of the tibia in adults we internally fix two-thirds of the compound fractures and only one-third of the simple fractures. There are no definite rules for selection; this represents a general tendency of the six surgeons to treat worse fractures more drastically.

The result of this policy has *not* been an overwhelming incidence of infection (*see* Table II). Although internal fixation of compound fractures resulted in an infection-rate two

TABLE II

Infection* in internal fixation:	
Simple fractures	4 in 67 (6%)
Compound fractures	7 in 47 (15%)
For comparison, infection* in compound fractures not internally fixed	4 in 30 (13%)

*Infection was defined as: cellulitis, delayed healing of wound, ulcer or sinus lasting over three months or requiring other major treatment or delaying union. There was no case of osteitis and no case of late amputation primarily due to infection. Infection. due to skin slough has been considered separately (*see* below re skin necrosis).

and a half times that of simple fractures, the compounding wounds may be becoming infected because they are compound and not necessarily because they are internally fixed. This is supported by the analysis of compound fractures *not* internally fixed which, on the same definition of infection, show a rate nearly as high. The 2% difference between the fixed and the conservatively treated compound fractures might be more than accounted for by our tendency to select the worse fractures for internal fixation and the less severe ones for conservative treatment. So far as these figures go there is, therefore, no substantiation for the belief that metal greatly increases the liability to infection in compound fractures.

This is not the whole story and it would be wrong to hide the following facts: When the analysis for sepsis was being carried out another complication came to light which proved to be much more serious. This was skin necrosis. Skin necrosis resulting in full thickness slough occurred in a disturbing number of cases. 7 out of the 8 late amputations in all fractured tibias were necessitated, partially or entirely, by skin necrosis and the infection that followed it. Although 2 of these 8 amputations had received conservative treatment it must be admitted that the incidence is higher among the internally fixed than among the conservatively treated fractures. The main argument of this paper remains unaffected since this complication is not due to the metal as such but only to the operation for putting it in. Whereas the problem of corrosion has almost been solved, however, the problem of skin necrosis still has to be dealt with before the internal fixation of fractures, simple or compound, can be considered really satisfactory.

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Dr. J. M. Zarek (London): *Some Engineering Considerations in Metallic Osteosynthesis*

Metallic osteosynthesis has been of great interest to the surgeon for many centuries. Petronius (*in* Bates, 1950) in 1565 used gold to repair cleft palates and in 1775, Lapeyode and Sicre (*in* Venable and Stuck, 1947) used metallic wires for the fixation of fractured bone. In this century the advances in metallurgy have stimulated the surgeon to make a more extensive use of new materials. Some of the new techniques proved to be successful but others resulted in failures exposing the existence of problems which were often not appreciated, and in any case seldom investigated. A great number of these problems are of a metallurgical or engineering nature, and, although of primary importance, for obvious reasons have received very little attention from the medical scientist.

Apart from the bio-mechanical problems affecting the bone a great number of problems exist with the implant itself. Here we have such problems as the material to be used, design, method of manufacture and the final treatment of the implant.

The mechanism of how metallic implants are tolerated by the living tissue is not yet fully understood. Clarke and Hickman (1953) surveyed the past literature and investigated *in vitro* the possibility of correlating the electrical potentials of metals and their behaviour in biological fluids and suggested that there was a relationship between the anodic back EMF, the corrosion of metals and their behaviour in the living body. Difficulties arise, however, from the fact that implants made of what would appear to be the same material do not behave in exactly the same manner from one case to another. In this country stainless steel of the 18/8 Type (FMB) has been used quite extensively in the operating theatre and examples of the use of this material will therefore be given to illustrate my thesis.

The following examples illustrate some of the points. Fig. 1 shows a Moore's stainless steel (18/8) hip prosthesis which failed a few weeks after insertion. Being of a complex and irregular shape it was made in two parts. The larger part of the sphere was machined and "force-fitted" and welded on to the lower part which, it appears from the macrograph (Fig. 2), was cast. Because of the lack of correct heat treatment the cast material in the lower part, after etching in aqua regia, shows a marked change in its structure suggesting a change of its physical properties. Also it shows much larger grain structure than the upper part. Points A and B show the weld. It is very important to remember that some stainless steels undergo structural changes when heated in the range of 500°–800° C. When a zone of the welded object reaches that range of temperature, its effect on the steel is referred to as "weld decay", and results in a rapid attack of grain boundaries in a corrosive medium. The part at C, D and E, because of the sudden change of cross-sections, is liable to "freezing in" of internal stresses during the non-uniform process of cooling. Points C, D and E show a high degree of intergranular corrosion of the material which is due to the effect of the above factors.

Fig. 3 shows an acrylic prosthesis of the upper part of the femur in which an intramedullary



FIG. 1.—Stainless steel Moore's prosthesis.



FIG. 2.—Macrograph of the section of the upper part of the prosthesis shown in Fig. 1.



FIG. 3.—Acrylic replacement of the upper part of the femur with a stainless steel intramedullary nail.

stainless steel nail was used as a method of fixation. When the prosthesis failed examination of the nail showed high degree of corrosion of the part (A) which was covered by the plastic while that part which was in direct contact with the bone or tissue was unattacked. In this example the part of the nail covered by the plastic, because of differential oxygenation, has become anodic (lack of oxygen) in relation to the rest of the nail and caused rapid corrosion.

The above simple examples show how important the problem of design and manufacture of a prosthesis is towards a successful surgical procedure. From the engineering point of view further problems, such as fatigue or stress corrosion, are sufficiently well understood to be considered in design. However, in relation to the reconstruction of the human body further points must be considered. At the present moment we do not have a criterion of compatibility of metals to the living cell, we do not know yet why some materials although non-toxic cause post-operative complications. The answer may lie within the field of surface potentials of metals and the electrical properties and the requirements of the living cell.

It is known that when a metal is immersed in an electrolyte a potential difference is set up between the metal and the solution. We have found that the surface potential of stainless steel depends not only upon its composition but also upon its mechanical state and the treatment of the surface during the polishing process.

Experiments (Zarek, 1957) have shown that the surface potential of stainless steel is affected by mechanical working and by the type of polishing used in the finishing process.

Further, it may be of interest to note that stress, whether static or fluctuating, not only increases the rate of corrosion, but has also a very marked effect upon the surface potentials.

Finally, to emphasize the interdependence of some of the factors discussed above let us analyse some of the less obvious problems involved in the use of such a simple implant as a screw and a plate. First let us consider the shape of the thread to be used. The conventional V-shaped form of thread used in engineering is an ideal "stress raiser", producing at the root a high concentration of stress. In engineering practice it is accounted for by using a sufficiently large screw to carry safely the required load. In the human body this would mean larger degree of interference with the living system. So the shape of the thread to be used in bone should be such as to produce as little stress concentration as possible and to keep the size of the screw to a minimum. Further, the fact that concentration of metallic ions at the root of the thread, when in situ, may be different from that at the top of the thread and so establish a gradient of potential resulting from the changes of concentration polarization should not be overlooked. Fig. 4, a photo-elastic model subjected to uniform bending, shows that the effect of a V-shaped thread on the stress concentration in the core of a screw is much greater than in the rounded thread.



FIG. 4.—Photo-elastic model subjected to pure bending showing the effect of shape of notch (or screw thread) on stress concentration.

In present-day practice the lower surface of the head of the screw is conical in shape to fit the countersunk part of the plate. Corrosion is frequently set up in that part of the screw and plate. However well the plate and the screw may be matched, it is difficult to drive in the screw so that the conical surface of the head of the screw will be in continuous contact with the plate, as this will only happen when the longitudinal axis of the screw is at a right angle to the plate. All other positions will give a local contact between the screw and the plate and so produce a high pressure point of contact, causing local plastic deformation of the metal and subsequent corrosion. A spherical surface of contact between the screw and the plate would minimize this source of trouble.

Finally—the screw and the plate should be subjected to a surface treatment which will produce in both the same potential and of the required magnitude for the body to tolerate it. But what is the required value? The answer to this question must come from the biological scientist and then the complex problem of compatibility will no longer be studied in isolation (Zarek, 1957).

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Section of Physical Medicine

President—A. C. BOYLE, M.D., M.R.C.P.

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DISCUSSION ON THE CLINICAL AND RADIOLOGICAL ASPECTS OF SACRO-ILIAC DISEASE

Dr. M. Thompson: It is unusual for the sacro-iliac joints to be spared in ankylosing spondylitis, although such cases do undoubtedly occur, and account for approximately 1% of all patients with the disease. Thus Hench *et al.* (1947) quote 9 such patients in a series of 1,035; Knuttson (1950) 1 patient in a series of 147; Forestier *et al.* (1956) 2 patients in a series of 200. In my own experience of 163 patients I have known 2 such cases. The first of these patients was a woman aged 52 years with a history of peripheral arthritis and spondylitis dating from the age of 32, associated with severe psoriasis. She was anæmic and debilitated, and had ankylosis of cervical, thoracic and lumbar spines, but the sacro-iliac joints were unaffected. The second patient was a man aged 66 years who had suffered from a peripheral arthritis of the rheumatoid type for eighteen years. Classical spondylitic changes in the cervical region had developed later; the remainder of the spinal column and the sacro-iliac joints were spared.

These occasional atypical examples of spondylitis can be distinguished, on radiological and clinical grounds, from the group classified by Forestier and Rotes-Querol (1950) as suffering from senile hyperostosis of the spine.

Reference must also be made to senile changes in the sacro-iliac joints. Fibrous obliteration of these joints, occurring more or less as a normal phenomenon of advancing age, has been described (Romanus and Yden, 1955). This process leads to immobilization by intra-articular ankylosis. These changes alone do not result in radiographic obliteration of the joints, but only in narrowing of the joint space. The diagnosis of senile obliteration of the sacro-iliac joints should not be considered until full clinical and radiological evidences of spondylitis have been sought and proved absent.

In ankylosing spondylitis, sacro-iliac and vertebral symptoms may be slight, and indeed gross changes leading to complete synostosis of the joints may occur in the total absence of symptoms:

A miner, aged 31 years, was admitted to hospital suffering from a dislocated femur as the result of a motor-cycle accident. X-ray of the pelvis revealed complete synostosis of the sacro-iliac joints due to ankylosing spondylitis. Further X-rays of the remainder of the spine revealed a "poker-spine" with gross syndesmophyte formation. This patient had worked uninterruptedly as a coal-hewer in low pit seams. The only features of note in his previous medical history were an episode of duodenal type of dyspepsia and an illness characterized by gross anæmia, refractory to oral iron, but which responded to intravenous iron.

However, the vast majority of patients suffering from sacro-iliitis do have symptoms. These consist chiefly of intermittent attacks of dull, deep-seated pain in the distribution of the I and II sacral nerve roots. The principal localization of the pain is in the upper and medial quadrant of the buttocks with radiation towards the hips and the posterior aspects of the thighs. The pain is frequently nocturnal or vesperal. It is occasionally sharp and acute attacks may be precipitated by vibratory shocks to the spine or by exercise after prolonged sitting, or by both, as following a long car journey. Running is awkward and a hard kick at a ball is painful or impossible.

Stiffness is a marked feature, and usually spreads in a band-like distribution across the sacrum and buttocks as far as the hips. Occasionally the patients complain of a feeling of weakness. The changes in the sacro-iliac joints are nearly always bilateral and often approximately symmetrical; but authentic instances of unilateral sacro-iliitis have been recorded in spondylitis, and unilateral disease may persist for months or even years.

There appears to be little or no correlation between the clinical and radiological severity of the lesions. Patients may be seen with comparatively minor sclerotic lesions, but with marked pain and systemic disturbance. By contrast, others may have gross and typical radiological changes of sacro-iliitis but suffer only minimal intermittent symptoms and have normal or near-normal spinal function on clinical testing.

Reference has been made by several authors to a pre-spondylitic phase in which symptoms and signs may precede radiological evidence of sacro-iliitis:

A female patient aged 25 years who had suffered from low back pain for eighteen months had already had 2 negative X-rays taken for clinically suspected ankylosing spondylitis before a film revealed dense osteo-sclerotic lesions in the regions of both sacro-iliac joints. Erosions and pseudo-widening were demonstrated by oblique views, and the subsequent course of the illness, with progressive symptoms and signs, raised E.S.R. and anæmia, gave full confirmation to the diagnosis of ankylosing spondylitis.

Physical signs may be present at this stage of the illness, i.e. the phase of sacro-iliitis, but Boland and Present (1945) found them in only 50% of their series of 100 patients. Forestier *et al.* (1956) elicited signs of the "sacro-iliac syndrome" in 47% of their 200 patients.

The patient may walk with a limp or with a slightly stiff waddling type of gait and there may be wasting of the gluteal muscles. Local tenderness, when present, is found just below and medial to the posterior superior iliac spines, over the only part of the auricular cartilaginous portion of the joint that is not completely protected by bone. Numerous manœuvres used to induce pain on mobilization of the sacro-iliac joints have been described (Table I). None of them is absolutely pathognomonic of sacro-iliac disease;

TABLE I.—TESTS FOR SACRO-ILIAC DYSFUNCTION

Erichsen
With patient supine on a firm surface, the anterior superior iliac spines are pressed towards each other. Pain provoked in the sacro-iliac region(s) indicates a positive test.

Fabere sign (Patrick)
With patient supine, the leg is flexed at knee and hip, abducted, externally rotated and then, with the pelvis steadied by a hand on the contralateral anterior superior iliac spine, the hip is pushed into a position of extension. Pain is provoked in both hip and sacro-iliac disorders.

Gaenslen
Patient lies on one side and flexes the underlying thigh and knee. The examiner then hyperextends the upper leg with the knee extended. If pain is produced, it indicates a lesion of the sacro-iliac joints on the hyperextended side.

Laguere
With patient supine, the knee is flexed and the hip flexed and abducted. The examiner then presses down upon the contralateral anterior superior iliac spine, and upon the flexed knee. The adductors of the hip are put under tension and the iliac portion of the sacro-iliac joint is forced against the sacral surface.

Lewin
With patient supine on a firm surface, the examiner exerts pressure on both anterior superior iliac spines, forcing them laterally. This puts a stretching force upon the anterior sacro-iliac ligament.

Mennell
Tenderness just medial to the postero-superior iliac spine, indicating a lesion of the superior sacro-iliac ligaments.

Yeoman
With patient prone, the knee is flexed, a firm grasp taken of the ankle and the hip pulled into extension. The examiner's other hand is placed over the contralateral sacro-iliac joint to fix the pelvis. This manœuvre stretches the anterior sacro-iliac ligament and elicits pain in a lesion of the joint.

some are non-specific, and their interpretation may be difficult. The corresponding hip or the lumbo-sacral articulation may well be mobilized simultaneously; so that unless it is certain that there is no disease of these structures and unless the patient can accurately localize the induced discomfort to the sacro-iliac joints, the tests are negative. These manœuvres are designed either to manipulate the obliquely situated joint surfaces in a shearing or scissors-like action, or else to separate the anterior or posterior margins of the joints.

The actual radiological progression of changes in the sacro-iliac joints in ankylosing spondylitis is now well known. The process is initially patchy and destructive, the joint margins become ill-defined usually in the lower or central portions of the iliac surface; with blurring of the otherwise sharply defined subchondral bone. Pseudo-widening of the joint occurs at this stage owing to marginal decalcification and then marginal erosions; and scattered patches of decalcification along the linear margins of the iliac surface may give rise to the rosary effect described by Scott (1942). At the same time, varying degrees of sclerosis and new bone formation occur with bridging of the joint. This marked polymorphism of the radiological signs correlates well with the observed pathological features of the disease; inflammatory, destructive and reparative processes occurring simultaneously within the same joint. When healing is complete, the joint space becomes completely bridged and obliterated. At this stage, sclerosis decreases and ultimately the area becomes osteoporotic.

The evolution of the full range of sacro-iliac joint changes may vary from a few years to twenty years. Indeed, sometimes the changes appear to become arrested and this is especially liable to occur in women, in whom restricted and abortive cases of spondylitis have been described (Thompson, 1954).

Sacro-iliitis occurs not only in classical ankylosing spondylitis, but in several other conditions, listed as syndromes of pelvo-spondylitis (Table II).

Pelvo-spondylitic, and especially sacro-iliac, changes occur in psoriatic arthropath-

TABLE II.—SYNDROMES OF PELVO-SPONDYLITIS

Ankylosing spondylitis	Syphilitic
Reiter's syndrome	Post-recurrent rheumatic fever
Psoriatic arthropathy	Familial with arterial calcification
Brucellosis	Post-juvenile rheumatoid arthritis
Fluorosis	Associated aortic valve disease; iritis;
Paraplegic	and peripheral rheumatoid disease

The lesions vary from typical gross and diffuse ankylosing spinal changes to localized sclerotic lesions in the sacro-iliac joints. Their presence may be clinically overshadowed by changes in peripheral joints. In a personal series of 30 patients suffering from psoriatic lesions and arthropathy, sacro-iliac lesions were identified in 8, i.e. 26·6%. Wright (1956) identified abnormal changes in 37% of his 32 patients with this disease.

A similar pelvo-spondylitic syndrome may occur in Reiter's disease. At present the radiological features alone do not appear to suffice to differentiate the psoriatic or post-urethritic types of pelvo-spondylitis from classical examples of ankylosing spondylitis but further study of larger series of patients may reveal some distinctive patterns and points of differentiation.

One other condition characterized by roentgenographic sacro-iliac changes is *osteitis condensans ilii*, first described by Sicard *et al.* in 1926. The radiological appearances consist essentially of osteo-sclerotic lesions principally occurring in the lower margin of the iliac portion of the joint. The joint margins remain intact, though the sacrum may also be involved. The changes may be unilateral or bilateral.

The principal points of differentiation between osteitis condensans ilii and ankylosing spondylitis are shown in Table III. Radiographic oblique views, postero-anterior views

TABLE III.—PRINCIPAL POINTS OF DIFFERENTIATION BETWEEN OSTEITIS CONDENSANS ILII AND ANKYLOSING SPONDYLITIS

Osteitis condensans ilii	Ankylosing spondylitis
Rare in males	Predominantly in males
Onset after pregnancy common	Onset not related to pregnancy
Chief symptom is pain; stiffness not marked	Stiffness often as marked as pain
Restriction of spinal movements slight or absent	Restriction of spinal movements commonly present
Lesions may be unilateral	Unilateral lesions very rare
X-rays show dense sclerotic lesions on lower margin of iliac border, with less common sacral lesions. Joint margins intact	X-rays show marginal decalcification of joint; loss of definition of the subcortical bony layer; patchy sclerosis and pseudo-widening of the joint space
Other radiological lesions very rare and probably not significant	Coincident radiological evidence common in spine and other joints, or develops later
Systemic symptoms absent	Systemic disturbance common
E.S.R. normal	E.S.R. raised

and tomography have been used in order to demonstrate the joint margins and the extent of the lesions.

The nomenclature "osteitis condensans ilii" has little to commend it. There is no evidence of osteitis on histological examination of affected tissue (Baker, 1953), and the changes are not restricted to the ilium, the sacrum commonly being involved. Sacro-iliac osteosclerosis would be a preferable term.

The status of the condition as a disease entity is still in question. No theory of ætiology has proved to be completely satisfactory. Thus it has been ascribed to urinary infection (Szabados, 1947), osteo-chondritis (Ude, 1952), post-partum endarteritis of the iliac vessels (Gillespie and Lloyd-Roberts, 1953), ante- and post-partum ligamentous relaxation (Hare and Haggart, 1945), atypical ankylosing spondylitis (Baker *et al.*, 1950) and trauma (Shafar, 1953; Layani *et al.*, 1951). It may be that several entities are encompassed within the framework of this unusual sacro-iliac lesion.

Although the majority of authors consider that osteitis condensans ilii can cause back pain and therefore deserves consideration as a clinico-pathological entity, doubts have been cast by others who feel that it is an osteosclerotic condition of no clinical significance. Occasional lack of correlation of symptoms with the site or dimensions of lesions demonstrated radiographically is not altogether surprising as such discrepancies occur in ankylosing spondylitis and, indeed, it might be expected that the most painful phase would occur prior to the development of the sclerotic lesions.

Further clinical, pathological and serial radiographic studies may shed more light on the natural history, but in this respect it is necessary to observe some caution. Serial roentgenographic examinations of the female pelvis should not be lightly undertaken in

pregnant women or women of child-bearing age (M.R.C. Report, 1956; Stewart *et al.*, 1956). Even in the male, there are dangers in irradiation of the gonads. Some reorientation of our attitude may be needed in respect of the treatment of ankylosing spondylitis by deep X-ray therapy, especially in patients suffering from mild or restricted forms of the disease who might be equally well treated by methods invoking no risk.

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Dr. D. R. L. Newton: During the past ten years so much attention has been focused upon various manifestations of ankylosing spondylitis that many people now appear to believe that symptoms peculiar to spondylitis are, in fact, intrinsic manifestations of sacro-iliac disease, and perhaps some of those who deal with rheumatic disorders may not pause sufficiently often to examine fundamental issues.

Shipp and Haggart (1950) believe that the sacro-iliac joint is an amphi-arthrosis, or, in modern terminology, a secondary cartilaginous joint, but the classical work of Sashin (1930) has more recently received confirmation by Macdonald and Hunt (1952), and there can be little doubt that the joint is of the primary synovial type. It is not difficult to see why anatomical interpretations should have differed so widely. The normal life-history of the sacro-iliac joint conforms essentially to the same pattern of degenerative changes that occur in peripheral joints. After the third decade there is usually an irregular loss of superficial cartilage, with fibrillation, later leading to erosions of varying size. But the fact that the joint is exposed to tremendous compressive force with only very slight movement probably determines the more unusual result ending in a varying degree of fusion. This may occur because the opposing cartilage surfaces are firmly fixed together by debris, rather as if glued together, or because extensive areas of degenerated cartilage are replaced by a loose vascular connective tissue: in either case X-rays appear normal. True bony ankylosis never appears to occur except as the result of acquired disease.

In man, the sole function of the sacro-iliac joint would seem to be to act as a shock absorber at a point where the redistribution of weight occurs. Experiments performed in different ways by Sashin and by Macdonald and Hunt suggested that the only movements that occurred were a very slight degree of gliding, and minimal rotation about a fulcrum set approximately at the level of the second sacral segment. It appeared that no significant degree of subluxation could occur in the adult male except as the result of trauma interfering with the normal joint mechanics. In the absence of the muscle control available to most other joints, the stability of this joint depends solely upon the arrangement of its ligaments. Simple clinical tests may therefore give as much indication of an "irritable" joint as does the production of pain by the application of tension to the capsule and associated ligaments of an actively diseased peripheral joint.

The nerve supply of the sacro-iliac joint is derived from the I and II sacral nerves, from the superior gluteal nerve (L4, 5, and S1), and probably also directly from the lumbo-sacral trunk. A study of the arrangement of the sclerotomes and myotomes of the lower extremity will show why deep pain reference from the sacro-iliac joint may vary so considerably in distribution. Pain of typical "root type" accurately referred to dermatomes and perhaps accompanied by paræsthesia does not occur unless the lumbo-sacral plexus is secondarily involved by a pathological process arising from within the joint. It is important to realize that so far as quality and localization are concerned, there is nothing to distinguish deep pain arising in the sacro-iliac joint from deep pain resulting from a

lesion of comparable severity involving other structures receiving their nerve supply from the fourth lumbar to second sacral segments.

The early diagnosis of sacro-iliac disease may be of more than purely academic importance. Support for this principle may be found, for example, in the advances which have taken place in the management of tuberculosis and malignant disease. Hart and his colleagues (1949) drew attention to the improvement which frequently occurs in patients suffering from ankylosing spondylitis when a firm diagnosis is made and the nature of previously obscure symptoms explained. Unnecessary deformity may undoubtedly be prevented by commonsense management from an early stage in the disease, and some authorities believe that the process may actually be slowed down by early radiotherapy. Sharp and Eason (1954) reviewed the place of radiotherapy in the treatment of ankylosing spondylitis, and concluded that the probability of improvement was higher in patients whose symptoms were of short duration and in those in whom radiological changes were confined to the sacro-iliac joints.

The nature of many of the disorders which affect the sacro-iliac joints will become apparent on routine X-ray films, and most people will agree with the wisdom of making a radiological examination in every case complaining of low back pain or "sciatica".

Seddon and Strange (1940) in reviewing 176 cases of sacro-iliac tuberculosis found it to be a disease of young adults and with an equal sex incidence. The most frequent presenting complaints were sciatica, pain in the hip, and in the lumbar region. Buttock and thigh pain was rare. The disease was bilateral in only 5 cases, and associated tuberculosis was more common in the lumbo-sacral spine and hip than in the dorso-lumbar region, which is the most usual site of uncomplicated tuberculous disease of the spine.

"Sacro-iliac strain" is a not uncommon diagnosis, particularly in post-partum women. Many cases so labelled in fact present the history and physical signs of some form of intervertebral joint strain or derangement, often dating from their return to their normal household chores; others are certainly cases of ankylosing spondylitis or *osteitis condensans ilii*.

Osteoarthritis of the sacro-iliac joint is a common radiological finding and is frequently associated with old trauma in the region of the joint, with contralateral hip disease, and with an asymmetrical type of transitional lumbo-sacral vertebra. Sacro-iliac osteoarthritis appears to be either symptomless or completely overshadowed by symptoms more directly attributable to the predisposing condition.

An extraordinary lack of awareness of the early manifestations of ankylosing spondylitis still seems to prevail outside Departments of Physical Medicine and others dealing mainly with rheumatic disorders. During the course of a long-term follow-up study at St. Thomas's Hospital, the author has found that the average length of time taken to reach the diagnosis of ankylosing spondylitis is a little more than six years from the onset of first symptoms. Many of these cases had been given loose diagnoses, such as sciatica, rheumatism and fibrositis, and treated by many methods in various places. In the case of patients first seen in the Physical Medicine Department at St. Thomas's, not having been previously investigated or treated elsewhere, the average time taken to reach the correct diagnosis was nine months from the onset of the first symptoms. This great discrepancy exists in other centres, too, and must be accepted as evidence that the average physician and surgeon is still unaware that many cases bear no resemblance whatsoever to the classical textbook description of the disease.

Hart and his colleagues (1949) enunciated their four cardinal diagnostic features of ankylosing spondylitis, these being spinal stiffness, diminished thoracic expansion, raised B.S.R., and radiological sacro-iliac changes. A number of early cases will probably be missed if these signs, important though they may be, should universally be regarded as early, and invariably associated, manifestations of the disease.

The comprehensive review of the varied symptomatology of ankylosing spondylitis given by Baird (1955) is worthy of careful study. Among the most important features must be mentioned the alternation of buttock and thigh pain from side to side; the aggravation of symptoms after rest, particularly first thing in the morning, after which stiffness is "worked off"; the various forms of chest tightness and soreness; and tenderness of bony points, particularly the ischial tuberosities. Moreover, in the presence of other good evidence, a diagnosis of ankylosing spondylitis should not be discarded just because the patient is a female, or over 35 years of age.

Bickbeck and his associates (1951) drew attention to the importance of iritis as a presenting symptom in ankylosing spondylitis. It now seems that by the time the eye disorder appears other evidence of spondylitis is usually manifest to those who know where to look for it, and iritis is in fact the occasion for the diagnosis and seldom the presenting symptom. An unexplained iritis or large joint swelling, particularly if involving the knees, should always direct attention to the sacro-iliac joints.

The painful heel is now a well-known feature of spondylitis, and Davis and Blair (1950) suggest that all men between the ages of 18 and 30 presenting with calcaneal periostitis and spurs have spondylitic changes in their sacro-iliac joints.

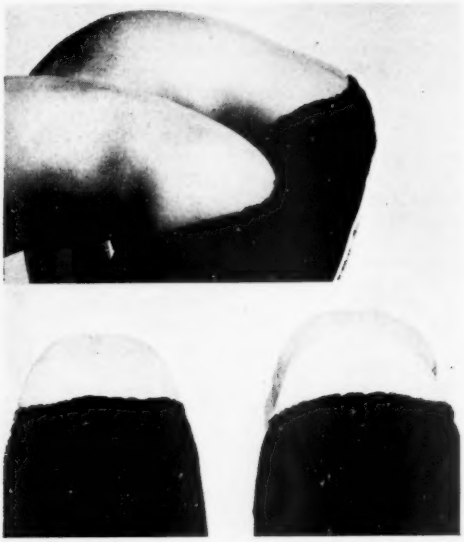


FIG. 1.—Normal control (behind and right) and spondylitic patient (front and left) bending to touch their toes.

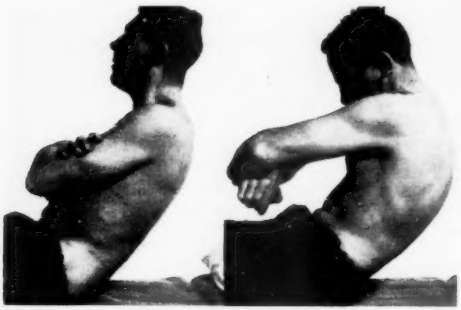


FIG. 2.—Spondylitic patient (left) and normal control rising from the supine position without the aid of their arms.



FIG. 3A, B and C.—Clinical sacro-iliac tests.

Posterior calcaneal bursitis is another frequent accompaniment and was the presenting symptom in a man of 64 years of age seen recently. He had had a duodenal ulcer for twenty years, a gastro-enterostomy five years ago followed by a stomal ulcer, and was now regarded as somewhat neurotic because of his many aches and pains. He had had calcaneal bursitis for a year, some chest soreness for six months, and recently some morning backache and pain in the right thigh, which he said he could "work off" by breakfast time. Clinical sacro-iliac tests were strongly positive and X-rays (previously reported as normal) showed bilateral spondylitic changes in the sacro-iliac joints. He also had symptomless bilateral calcaneal spurs.

One very common misconception is that a man who can touch his toes cannot be suffering from ankylosing spondylitis. It may, in fact, be very difficult to decide when there is limitation of lumbar spinal movement, particularly in the presence of a normal dorsal spine and hip-joints (Fig. 1). Cyriax (1954) has pointed out that lateral movements may be the first to appear reduced. Richardson (1955) has observed that the early spondylitic may only show obvious loss of lumbar mobility when he attempts to sit up from the supine position unaided by his arms (Fig. 2). Both these signs may precede by a long time the well-known flattening of the lumbar spine with a dorsal kyphosis which so commonly occurs in spondylitis. This flattening is due to the absence of the compensatory lumbar lordosis that occurs in other conditions which cause a dorsal kyphosis.

With the exception of bony points in ankylosing spondylitis, tenderness is a most inconstant and unreliable sign in sacro-iliac disease.

The clinical sacro-iliac tests described here have proved negative in all cases of sacro-iliac ankylosis, or in those where the disease has been present for many years and is presumably quiescent. Correct indication of which joint was actively involved was given in a high proportion of the cases in my series during the first four to five years that the disease was present. False positives have been rare and usually due to errors of interpretation. Many of the tests described in the literature involve either putting the lumbar spine into a position of strain, or placing a stress on other structures, such as the hip-joint. There is considerable disagreement as to the method by which these various tests should be performed, despite the fact that to be of value they should be simple in their application. No attempt appears to have been made to work out a simple method or to correlate the results thereby obtained with clinical, radiological and pathological findings. A detailed description of our tests is therefore given:

The first two tests are quickly performed while the patient is lying supine (Fig. 3A, B). In the first, the examiner applies pressure firmly, in a posterior direction, on both ilia in the region of the anterior superior spines; and in the second, laterally on the iliac crests, the application of pressure being towards the mid-line of the body. The surface on which the patient lies must be firm because otherwise no stress differential will be created between the anterior and posterior parts of the pelvis. In bed, for instance, the whole pelvis will sink back as one piece, concurrently placing a flexion strain on the lumbar spine. This is one common reason for a false negative result, and may be avoided by the use of fracture boards, or even the floor. A positive result is indicated by pain referred *laterally* into the lumbo-sacral or sacro-iliac region, into the buttock, or into the thigh. A patient with a low threshold for discomfort may wince, and on enquiry will state that it hurt him at the site of pressure; alternatively he may complain of mid-line tenderness where the sacrum was in contact with the surface of the couch. These complaints do not, of course, constitute a positive finding. In patients with a marked lumbar lordosis it will be necessary to fill in the space between the couch and the lumbar spine with a folded blanket or small pillow thus eliminating any concomitant lumbar spinal movement. The third test is performed with the patient lying prone (Fig. 3C). Pressure is applied to the central part of the sacrum by the "heel" of the hand. As in the other two tests, a positive result is indicated by *lateral* pain reference.

In all three tests the pressure must be applied evenly and with gradually increasing force, though at the final point of the antero-posterior and postero-anterior tests the examiner may be using almost his entire body-weight. Any attempt to apply force suddenly, or with a jerk is likely to cause unwanted lumbar spinal movement, and may lead to a false positive result. In cases in which marked activity is present in the sacro-iliac joint the sudden application of great pressure produces severe pain; in these cases quite gentle pressure evokes sufficient response for the interpretation of the test.

It has been found that when all three, or two together of these three tests, are positive it is almost always possible sooner or later to demonstrate radiological abnormality of the joint. One positive test out of the three should not immediately be dismissed as irrelevant, since this has occurred in some patients in whom radiological abnormality has later appeared, and in others in whom activity has been somewhat dubious though radiological abnormality was undoubted.

The survey referred to in this paper was aided by a grant from the Endowments Fund of St. Thomas's Hospital. I wish to thank Dr. P. Bauwens and Dr. J. H. Cyriax for their advice; Dr. J. W. McLaren for providing radiological and other facilities in his Department; and the radiographers for much time-consuming work. I am particularly indebted to Dr. R. G. Grainger, who has been entirely responsible for the radiological work involved in the survey.

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Dr. Ronald G. Grainger (St. Thomas' Hospital, London): *Radiological Aspects of Sacro-iliac Arthritis*

The sacro-iliac joint is the most difficult major joint both to demonstrate and to interpret radiologically. The radiographic technique is so important that I shall begin by emphasizing some of the more important technicalities.

For a satisfactory projection of the whole length of the sacro-iliac joint, the central X-ray must always be directed perpendicular to the plane of the sacrum, and the X-ray tube must be tilted to a degree dependent on the lumbo-sacral lordosis.

Fig. 1: These two films were taken of the same patient, supine on the table. A is taken with the tube at right angles to the table top (the usual lumbar spine or pelvis projection) and shows marked foreshortening of the sacro-iliac joint. B is taken with the tube angled upwards at 45 degrees and shows the full length of the joint, and consequently a much better joint space. We must not assess the sacro-iliac joints on films taken for the lumbar spine or for the pelvis if there is an appreciable lumbar lordosis, for, apart from the foreshortening, the joints will be considerably under-exposed. Films must be well penetrated as under-exposure may either obscure early joint changes or may simulate disease.

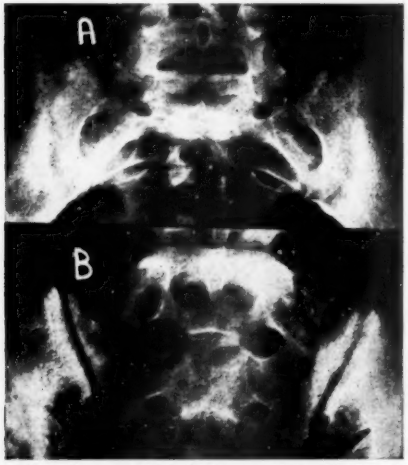


FIG. 1.—A, Central X-ray perpendicular to table top, demonstrating foreshortening and under-exposure of the sacro-iliac joints. B, Central X-ray perpendicular to sacrum of same patient, demonstrating the full length of the sacro-iliac joints.

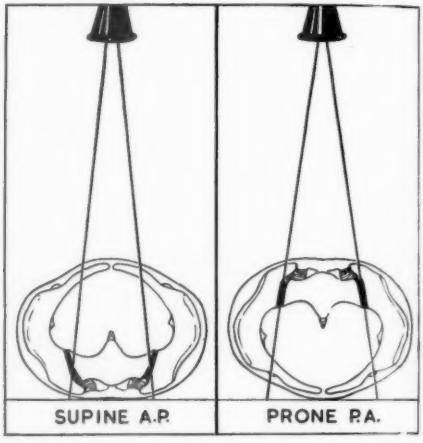


FIG. 2.—Demonstrating the geometric advantage of the prone over the supine projection.

The sacro-iliac joint approximates to a *plane joint* and the X-ray beam should ideally pass in this plane, parallel to the articulating surface and straight through the joint space.

Fig. 2: This objective is much better achieved by placing the patient in the *prone position* (P.A.), for in this position the diverging X-rays tend to pass *through* the divergent joint spaces instead of *across them* as happens in the supine position (A.P.), which is the standard projection. Because of the increased object-film distance, a fine focus X-ray tube should be used (if possible) to secure good bone detail.

Oblique views.—These are often unsatisfactory, particularly in spondylitis, because the obliquity of the joint space varies (from 3 degrees to 37 degrees) from patient to patient, from one side to the other in the same patient, and always considerably in the same joint according to the level of cross section.

In fact, it may be an anatomical impossibility to obtain a satisfactory single oblique view of the whole joint. Oblique films are of considerable value in sclerotic conditions which provide radiographic contrast with the joint space, but their diagnostic value is not predictable and they seldom provide information which cannot be obtained from supine and prone films which are so much more reliably obtained.

Tomography is a very useful technique for demonstrating the joint space, cavitation of bone, sequestrum formation or the extent of bone sclerosis. It is of little value in visualizing fine bone detail or the articular cortex, and is therefore seldom useful in the early diagnosis

of spondylitic sacro-iliitis. Tomography is of considerable use in differentiating sclerotic spondylitic changes from *osteitis condensans* and also in the assessment of joint tuberculosis.

The juvenile joint.—The appearance of the sacro-iliac joint depends greatly on the age of the patient, for until the age of 17–25 years the subchondral white line of cortical bone cannot be visualized. The juvenile joint lies more in the sagittal plane and appears as a single, broad, poorly-defined fissure, without a limiting line of articular cortex but with a finely-serrated bone margin (Fig. 3). In the mature joint the articular cortical bone is well defined and can be seen, on good films, as a thin white line in nearly every joint. The varying obliquity of the joint can be recognized in the A.P. and P.A. films, the anterior joint border being of course on the outer side. The upper posterior bone margins (A, B) are *not* in the synovial joint, but are united by the posterior fibrous interosseous sacro-iliac ligament. There may sometimes be an accessory synovial joint at this site.



FIG. 3.—Normal sacro-iliac joints at 9, 11 and 30 years.
N.B.—A, B, are non-articular bone margins.

ARTHRITIS OF THE SACRO-ILIAC JOINT

Destructive arthritis of the sacro-iliac joint occurs in a variety of conditions but they fall naturally into two ætiological groups: (i) the so-called collagen group of diseases, led by spondylitis but also including Reiter's syndrome (in which it is a common complication), and rheumatoid arthritis (in which it is rare), and (ii) arthritis of known bacterial origin of which tuberculosis is the most important, but which also includes pyogenic (usually staphylococcal) infection, gonorrhœa and brucellosis.

The similarity of the radiological changes in the sacro-iliac joints and in non-articular peripheral bone (particularly pelvic) in such apparently different conditions as ankylosing spondylitis, Reiter's syndrome and paraplegic states, suggests the possibility of a common ætiological factor. This may well be a common mode of assault from a pelvic inflammatory focus (e.g. prostatitis) with lymphatic spread. I think that this possible ætiological factor in the pathogenesis of ankylosing spondylitis, has received, at least in this country, an inadequate investigation and an approach somewhat lacking in enthusiasm.

The following is a brief review of the radiological features of the most important member of each group—ankylosing spondylitis and tuberculosis.

Ankylosing Spondylitis

The radiological changes of all bone and joint lesions in ankylosing spondylitis closely reflect what appear to be the two essential pathological processes.

Table I: First, *the destruction of peripheral bone and c rtilage* by overacting inflamed

TABLE I.—JOINT CHANGES IN ANKYLOSING SPONDYLITIS

(1) Bone and cartilage destruction	A.—Loss of cortical white line	(2) Bone formation	A.—Para-articular sclerosis (mainly iliac)
	B.—Articular erosions		B.—Ligamentous ossification
	C.—Para-articular porosis and blurring		C.—Diminishing joint space
	D.—Widening of joint space	(3) Healing ..	A.—Completion of bony ankylosis
			B.—Loss of sclerosis
			C.—Reconstruction of normal trabeculation

pannus (or periosteal tissues) and secondly, *the metaplasia into bone* of these invading connective tissues. This osteoblastic metaplasia extends beyond the previous confines of the bone and results in bone ankylosis of joints and in the whiskery fringing of spondylitic osteopathy—best seen in the ischial tuberosities. Both processes go on simultaneously and when affecting joints stimulate a reactive sclerosis in the surrounding bone.

These are progressive but self-limiting processes and they result in healing with complete fixity of the joint. This loss of movement reduces the osteoblastic stimulus: the sclerosis disappears and gives way to osteoporosis. The new bone trabeculæ form in lines of

weight-bearing, continuous from sacrum to ilium, but sometimes remnants of the joint space and/or cartilage may persist radiologically as well as microscopically.

By the time most spondylitics present for radiological examination the sacro-iliac joints show definite involvement and radiological diagnosis is easy. With increasing clinical suspicion of the disease, more and more patients are now presenting with early, and perhaps equivocal radiological signs.

Early Radiological Signs

The thin line of subchondral articular cortical bone is destroyed in *any* destructive arthritis in *any* synovial joint, but this sign becomes more valuable in sacro-iliac disease because the radiological demonstration of this joint is so limited.

FIG. 4: This is *not* a case of spondylitis but is an acute staphylococcal arthritis and shows

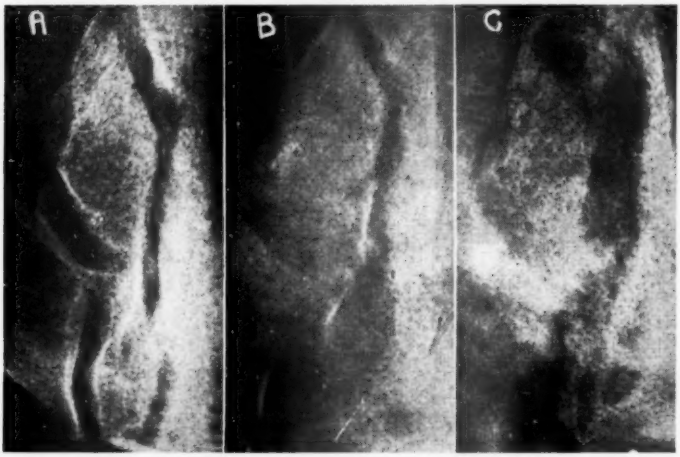


FIG. 4.—Progressive destruction of articular cortex in staphylococcal arthritis of the sacro-iliac joint. "A" shows joint before onset of disease.

the partial destruction of the articular cortex (B) prior to the complete disorganization of the joint (C). One can see flakes of cortex in process of destruction (B). This joint formed a staphylococcal abscess which invaded the pelvic cavity, involved both ureters, and caused death from uræmia.

Destruction of this white cortical line in spondylitis, usually occurs first on the anterior joint border on the iliac side, but the sacral cortex, particularly inferiorly and posteriorly may persist for some time.

Fig. 5: This patient presented with bilateral calcaneal fasciitis and spur formation and one year's history of low back pain. This film was thought by the first observer to be within normal limits but there is, in fact, loss of articular cortex leaving a finely serrated margin. Some articular cortex remains on the lower posterior part of the left joint.

Fig. 6: This patient developed his first low back pain in 1953 during a relapse of ulcerative colitis. This rather underexposed film, taken four months later, was reported by a most competent radiologist and accepted by the clinician, as being normal. There is, in fact, destruction of the iliac articular white line and a para-articular band of slight sclerosis. The change was bilateral and a diagnosis of ankylosing spondylitis is justified. Two years later the changes were quite obvious with a slight increase in joint space, blurred joint margins and a considerable increase in density of the sclerosis (which takes the identical pattern of the less-marked change, two years previously).

The finding of similar increase in joint space with blurred joint margins may resemble very closely the normal adolescent joint. If this change is bilateral and symmetrical in patients between 17 and 25 years, a final diagnosis may have to be deferred until more bone destruction or sclerosis has occurred.

Fig. 7: More localized destruction of bone may take the form of small articular erosions which may be arranged in rosary fashion. This patient has a two-years' history of low back pain. The erosions are predominantly unilateral (right-sided) in the lower ilium but there is bilateral sclerosis despite a normal joint space.

Following the destruction of articular cortex, the trabecular bone pattern of the ilium



FIG. 5.

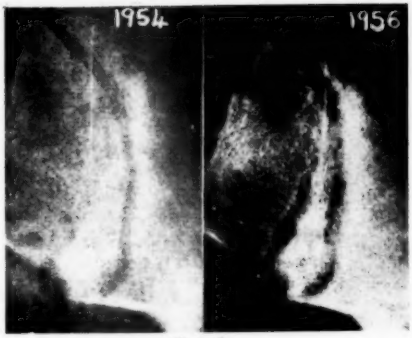


FIG. 6.

FIGS. 5, 6, 7, 8.—Four examples of early spondylitic sacro-iliitis (for individual details *see* text).



FIG. 7.



FIG. 8.

becomes blurred, sometimes porotic but usually sclerotic, and fine bone detail is lost.

Fig. 8: This man has had spondylitis for five years. The lower posterior sacral articular cortex is intact (right) but there is now a diminishing joint space, and a blurred woolly trabecular pattern in the poorly-demarcated iliac sclerosis.

Unilateral Sacro-iliac Involvement

Although the sacro-iliac changes are usually bilateral and symmetrical, spondylitis may first be radiologically manifest as a unilateral sacro-iliitis.

Fig. 9: This patient has had low back pain for two years with severe generalized restriction in spinal movement and a high B.S.R. Radiologically the left sacro-iliac joint is normal with a well-defined articular cortex throughout, but on the right side there is loss of the cortical line, slight increase in joint space, poorly defined articular margins and a blurred sclerotic bone pattern.

Fig. 10: This is another case of well-proven ankylosing spondylitis commencing as a unilateral sacro-iliitis, but there are now early sclerotic changes in the right ilium with a blurred and distorted trabecular pattern.

These early unilateral radiological changes may be indistinguishable from early tuberculous disease, but in the case of spondylitis the other sacro-iliac joint becomes involved within the next two or three years. This asymmetrical development may persist throughout the course of the disease. Tuberculous sacro-iliitis remains unilateral, progresses more rapidly and presents several distinguishing radiological features.

The three earliest signs in the radiological picture are: (i) destruction of the white line of articular cortex (particularly of the anterior iliac border), (ii) blurring of the joint margins and a blurred iliac trabecular pattern, and (iii) iliac sclerosis, usually in the caudal part of the joint.

If the clinical picture remains suggestive in the absence or uncertainty of these signs, it is

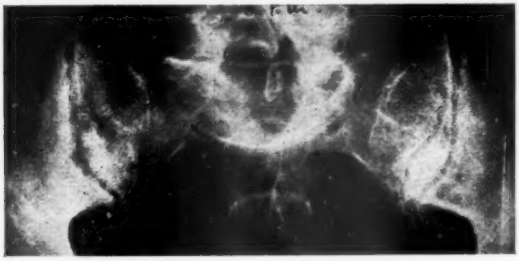


FIG. 9.

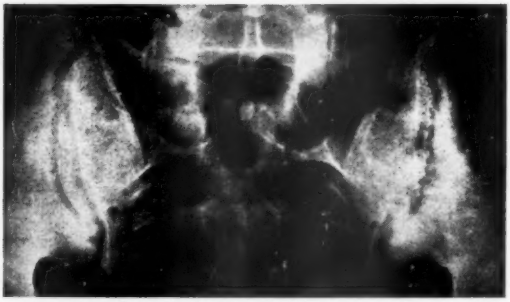


FIG. 10.

FIGS. 9, 10.—Two examples of ankylosing spondylitis commencing as unilateral sacro-iliitis.

important to maintain continuous radiological observation of the joints for as long as two to three years. There may well be this long delay before radiologically normal or doubtful joints show unequivocal signs of ankylosing spondylitis.

Tuberculosis of the Sacro-iliac Joint

A series of radiographs was presented demonstrating the radiological features of tuberculous disease of the sacro-iliac joint, emphasizing its natural history and progression, and the radiological features which distinguish it from spondylitic sacro-iliac disease.

The main differentiating features of the three commonest lesions of the sacro-iliac joint are summarized in Table II.

TABLE II

	Osteitis condensans	Ankylosing spondylitis	T.B. S.I. Joint
Age in yrs.	25–40	20–30	15–30
Sex	Female (95%)	Male (85%)	Equal
Symmetry	Usually bilateral	Bilateral (99%) symmetrical	Unilateral
Bone destruction	No	Yes	Yes: cavitating
Bone formation	Ilium. extensive defined	Ilium. sacrum ligaments	Ilium. sacrum
Joint space	Normal	Destroyed	Destroyed May be local
Sequestra	No	No	10%
Abscess + sinus	No	No	75% May calcify
Other skeletal lesions	No	Yes (80%)	Yes (40%)
Terminal state	No ankylosis	Slowly to bony ankylosis	Bony or fibrous ankylosis

Section of Surgery

President—ERIC A. CROOK, M.A., M.Ch., F.R.C.S.

[*March* 6, 1957]

DISCUSSION ON HYPOPHYSECTOMY FOR CANCER

Mr. Hedley J. B. Atkins (Department of Surgery, Guy's Hospital):

The Value of Hypophysectomy compared with Adrenalectomy for Advanced Cancer of the Breast

In 1945 Huggins (Huggins and Dao, 1953) performed total adrenalectomy on a series of patients with advanced cancer of the breast, but as all these patients died, they were not reported and I was unaware of this work when in 1947 I performed subtotal adrenalectomy on a series of 7 patients with advanced cancer of the breast who previously had had bilateral oophorectomy. The impression formed was that if sufficient adrenal tissue was removed to have an effect upon the breast cancer, the hazard to life was so great that it was not worth while doing, and this method of attack was allowed to lapse until it received fresh impetus from the discovery of cortisone which made total adrenalectomy safe. From then on, until 1953 when Luft and Olivecrona (1953) published details of encouraging results from hypophysectomy, adrenalectomy with bilateral oophorectomy became the standard method of treatment for all advanced cases of cancer of the breast for whom no further treatment by direct surgery, radiotherapy or hormone administration was admissible. The results were moderate and were similar to those which have now been reported from many centres all over the world.

Following this period, my colleague Mr. Murray Falconer began to operate upon certain of these cases by hypophysectomy; the choice of the operation being made at this time on grounds of expediency and depending very largely on which doctor sent the patient up and to whom the case was originally sent. It soon became apparent that this method of treatment was at least as likely to succeed as adrenalectomy and we decided in concert with Dr. K. S. MacLean, the Assistant Director of the Department of Medicine at Guy's, and my own assistant, Mr. J. L. Hayward, to compare the results of these two methods of treatment on a scientific basis (Atkins *et al.*, 1957).

The material which we used came from the Breast Clinic at Guy's, where we see approximately 80 new cases of breast cancer each year. When a suitable patient presented herself and a decision had been made that one or other of these operations was appropriate, the choice was made by a process of random selection. Paired cards, eventually to the number of thirty of each category, were placed in a box and whichever card was withdrawn, that operation was performed. In this way, a completely unselected series of 30 cases operated upon by adrenalectomy could be compared with 30 cases operated upon by hypophysectomy. No ethical problem was involved because we were all completely open-minded about the outcome of the investigation and we all would have been willing to have the choice of operation determined in this way had the decision involved our own relatives. It is only in the later stages of such an investigation, when one method of treatment appears to be drawing ahead of the other, that doubts of this sort begin to obtrude, but once started, it would be completely unethical to desist until the matter had been settled one way or the other beyond reasonable doubt.

We were fortunate at the Breast Clinic in that for the last six years we had used a method of assessing the results of treatment on cases of advanced breast cancer devised by Walpole and Paterson (1949) and known as the Mean Clinical Value (M.C.V.). M.C.V. assessment is particularly applicable to those diseases which, like advanced carcinoma of the breast, have many manifestations that show a varying response to treatment. It gives a numerical value to the effect of treatment which enables a clear-cut picture to emerge and one which can be compared statistically with other methods of treatment. The principle is to examine

all the manifestations of a case about to be treated and to measure them. These measurements may be made upon clinically obtrusive lesions such as lumps in the breast, the glands or the skin, by means of the direct application of calipers and tape measure to the part, or in the case of skeletal lesions they are made from the X-ray photographs. A base-line is thus devised for each lesion and any departure from this base-line as a result of treatment is assessed subsequently at four-weekly intervals. Subjective symptoms, with the exception of pain, are not used as factors in determining response to treatment, and pain is used only if the difference in degree of pain experienced is such as admits of no uncertainty.

Having established a base-line for each feature of the disease, the patient is started on treatment. In the cases under discussion this would be either by adrenalectomy with oophorectomy or by hypophysectomy. At each subsequent four-weekly visit, the lesions are severally assessed. If a lesion has undoubtedly improved it is given a mark of 2; if it has undoubtedly worsened: 0, and if it remains the same, or if there is any doubt: 1. The marks are then added and divided by the number of lesions to give an average mark for the response to treatment of the patient as a whole. The average mark would range between 0 and 2, and, being an awkward figure to handle, the result is multiplied by the factor 6 so that the range is between 0 and 12. It is this figure which is termed the M.C.V.

Having determined the M.C.V. for a patient at each four-weekly visit during treatment, a chart can be drawn of the patient's progress giving a picture of her response to treatment, impossible to achieve by the most careful description. Moreover, this sequence of numbers can be compared with the sequence of numbers derived from another patient treated perhaps by another method, so that the effect of treatment in the two cases can be readily contrasted.

In this enquiry, the method was extended so that a whole series of sequences derived from 30 patients treated by one method was compared with the whole series derived from the 30 patients treated by the other. In this way, approximately 1,000 integers derived from one series could be compared with 1,000 integers derived from the other and there was a chance that a statistical difference would emerge. Had we used, for instance, the number of months survived as an indication of response to treatment, only one integer would have been available for each patient—namely, the number of months survived. Consequently, in our series 30 integers would be available for comparison with 30 integers and it would be many years before differences could be detected on a statistical scale. Furthermore, the period of survival depends as much on the capricious nature of the siting of the secondaries as on their response to treatment. Thus a patient with a secondary in the brain that responded to treatment and then relapsed, might survive six months; whereas a patient with secondaries in the skin which never responded might survive eighteen months. The respective figures allotted to these patients on this basis would then give a misleading impression of the effect of treatment. It is true that in a very large series these anomalies would be ironed out, but it would prolong the investigation to such an extent as to rob it of any practical value.

As it is, our figures derived from the M.C.V. assessment are not conclusive. These figures have been analysed for us by Dr. P. Armitage of the Department of Statistics at the London School of Hygiene and Tropical Medicine, and although they are suggestive that hypophysectomy is to be preferred to adrenalectomy in the treatment of cases of advanced cancer of the breast, they are not statistically significant within the conventional range of 0·05 per cent.

There is, in fact, only a ten to one chance in favour of our results representing a real advantage of hypophysectomy over adrenalectomy, and not the twenty to one, or a hundred to one chance that we should wish to achieve before claiming that this was the case beyond all reasonable doubt.

Nevertheless, it looks very much as though hypophysectomy is going to be the better method of treatment; certainly the chances against it being less good than adrenalectomy are very great indeed. It looks as though, if you wish to disturb the rhythm of the endocrine orchestra, it is better to remove the conductor than the first violin.

Destruction of the hypophysis is certainly as effective as any method of treatment available to us at present for treating these desperate cases and it may well be better than any other. Because hypophysectomy is a relatively formidable procedure, two further considerations deserve our notice.

First, are there ways of destroying the hypophysis other than by direct surgical removal? Can we, as Lawrence and Tobias (1956) have indicated, destroy the hypophysis effectively by proton bombardment?

Secondly, is there not some pre-treatment test that can be applied to these patients to give some indication as to whether they are likely to respond?

In our laboratories at Guy's, Allen *et al.* (1957) have been working on this problem by estimations of the 17-ketosteroid secretion in the urine. If they have not solved this problem, they have certainly demonstrated a most exciting possibility, namely, that within a very short while we shall be able to say—"with this patient, destruction of the hypophysis is likely to succeed; with that patient it will be unavailing".

Whatever may be the possibilities for the future, I would wish to make the most earnest plea that they should be investigated on a scientific basis from the start and that good ideas should be tested out properly with adequate controls by random selection so that they become established or rejected within a reasonable time and do not linger on for decades until they expire of inanition.

The "radical mastectomy versus McWhirter" controversy is one that must not be repeated. Because there has been no proper control, we are no nearer the solution to this vexatious matter than we were when it was first mooted in 1942.

The place of hypophysectomy in the treatment of advanced cancer of the breast and its merits relative to other methods of hypophyseal destruction such as stalk section, the implantation of radio-active substances into the sella turcica, and proton bombardment, must be investigated in the spirit which would have informed John Hunter.

Surgeons particularly have been guilty of the gravest laxity of scientific discipline in their approach to therapeutics. We now have the tools, methods and techniques for instituting a neo-Hunterian era; let us do something about it.

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Mr. Murray A. Falconer (Guy's–Maudsley Neurosurgical Unit):

Hypophysectomy and Cancer

I propose to discuss the technique of hypophysectomy, to illustrate some of its results in advanced cancer of the breast, and to consider briefly its mode of action. Luft and Olivecrona in 1953 must be credited with the first concerted attempt to determine the effects of the operation in patients with cancer. Since then several surgeons have reported their results, notably Bronson Ray in the United States and Radley Smith in this country. There is now general agreement that the operation is only of value in advanced carcinoma of the breast and in a few cases of carcinoma of the prostate. It seems of no value in other tumours such as malignant melanoma, metastatic carcinoma of the gonads, or hypernephroma.

Surgical treatment.—Of the three possible surgical routes to the pituitary gland (trans-sphenoidal, sub-temporal, and sub-frontal), only the latter gives adequate exposure. The details of operative technique vary from clinic to clinic. We perform a right frontal craniotomy under general anæthesia, and then approach the chiasmal region by lifting the frontal lobe off the anterior cranial fossa, simultaneously sucking cerebrospinal fluid out of the chiasmal cisterns. The chiasmal region has always been readily visualized without recourse to hypotensive techniques, refrigeration anæsthesia, or preliminary lumbar or ventricular drainage. All arachnoidal tissue within the concavity of the chiasma is divided, exposing the pituitary stalk and the diaphragma sellæ. If the chiasma is prefixed, some extra room can be gained by chiselling off the tuberculum sellæ. The pituitary stalk can then be cut flush with the diaphragma without prior clipping, for it bleeds very little. Next the diaphragma is incised and the pituitary is then scooped and sucked out, sometimes in one piece, but generally in fragments. Some bleeding from the cavernous sinus surrounding the pituitary fossa may be encountered at this stage, but it is seldom profuse and generally stops spontaneously once the gland is removed. We then usually instil Zenker's fluid on a patty for 2 to 3 minutes, in order to fix any remaining glandular fragments before inserting a quick-setting acrylic plate to prevent reunion of the pituitary stalk to any glandular fragments that may have eluded removal and chemical fixation.

It is our practice to perform this operation under a high cover of cortisone starting with 50 mg. by mouth about six days before operation and working up to 400 mg. on the day of the operation. Following this regime the post-operative management has usually been

smooth, and the dose of cortisone is decreased in stages to 25 mg. twice daily by mouth on the 8th day, at which it is maintained. Provided the carcinomatous condition permits, the patient is allowed out of bed by the 5th to 8th post-operative day.

Results.—The results of hypophysectomy, in our cases, have been summarized by Mr. Hedley Atkins. All the patients had breast carcinoma with widespread metastases which had failed treatment by stilbœstrol, testosterone, or similar hormones after prior treatment by surgery or irradiation. 20 of the 30 patients showed some improvement in the early stages, but after the sixth month the majority began to show, at varying periods of time, reappearance or progression of their lesions. However, 2 of the 5 patients operated on longer than three years ago are still surviving. Both regressed and one is still without recrudescence, although the other after an interval of two and a half years has exhibited fresh lesions. The results prima facie in the hypophysectomy group seemed a little better than after adrenalectomy and several have been able to return to a normal life.

There were no deaths which could be ascribed to the operation, although three died within a month from the progress of their carcinoma. Certain complications, however, occurred:

(1) In one patient the operation was not practicable owing to an abnormal configuration of the sellar region. This patient was assessed as a failure for the operation, and was subsequently submitted to adrenalectomy.

(2) Some degree of diabetes insipidus developed in most cases, generally within the first post-operative week. Sometimes Pitressin, either as snuff or by injection, was required to control it during the early stages, but in all instances it declined spontaneously within a few weeks or months.

(3) Six patients had bitemporal visual field defects of varying degree on perimetry, but only one complained of her defective vision.

(4) All patients had anosmia on the side of operation, a few had bilateral anosmia.

(5) Most patients in the course of a few weeks became myxœdematous, and were then given thyroid 30 mg. twice daily by mouth.

Mode of action.—In those cases where the operation has failed to halt the disease, or where there has been a recurrence after a remission, a possible inference is that the hypophysectomy has been incomplete. Luft and Olivecrona (1953), and also Pearson *et al.* (1956) have accepted depression of the radioactive iodine uptake of the thyroid as evidence of the completeness of the hypophysectomy. In 19 of our cases we made these studies and found values which were consistently depressed to low or very low levels. Yet in 6 of our cases which came to post-mortem and then had the pituitary fossa carefully sectioned, fragments of anterior pituitary lobe variously estimated at between 1% and 10% of the total volume of the gland have been found histologically. One of these patients had benefited considerably from the operation and died following an accident some six months later. Thus in her case regression of the disease occurred in spite of the fact that her hypophysectomy was not complete.

It is possible that, in many of our other surviving patients, the hypophysectomy, although extensive, was likewise not complete. It may well be that pituitary stalk section alone can produce comparable results, due to interruption of the portal venous circulation from the hypothalamus to the anterior lobe of the gland. Further experience is required to settle this point.

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Mr. A. P. M. Forrest (University Department of Surgery, Western Infirmary, Glasgow):

Yttrium90 Implantation of the Pituitary

During 1955 we treated 45 patients with advanced malignant disease by the implantation of radon seeds into the pituitary fossa, a total dose of 10–20 millicuries (mc.) being inserted by means of a cannula introduced through the nose and sphenoidal sinus (Forrest and Peebles Brown, 1955; Forrest *et al.*, 1956). Our hope of selectively destroying the pituitary gland was not fulfilled, for the gamma radiations caused damage also to the optic chiasma and hypothalamus, producing serious loss of vision in 7 of the 45 patients and a high incidence of permanent and severe diabetes insipidus. In two patients who were admitted in coma nine months after implantation, typical radiation changes of fibrinoid necrosis of the hypothalamic blood vessels were found at post-mortem.

However, it was also apparent that, despite these grave disadvantages, a good remission

of disease could be obtained by this relatively simple method of treatment. No improvement occurred in 5 patients with malignant melanoma, 3 patients with cancer of the uterus, or 1 with sarcoma of the breast, but 10 of the 36 patients with breast cancer had objective improvement in tumour deposits as a result of the hypophyseal irradiation. 5 of these 10 patients are still alive and in remission—an average time of ninety-six weeks after implantation (Table I).

TABLE I.—PITUITARY RADON IMPLANT FOR ADVANCED BREAST CANCER

Jan. 1955—*Feb.* 1956 .. .. .. 36 *Cases*
Assessed Feb. 28, 1957
Cancer not improved
Dead .. .. 25 Patients
(Average duration of life since implant—12 weeks)
Cancer stationary
Alive .. .. 1 Patient
(Duration since implant—75 weeks)
Cancer regressed
Alive .. .. 5 Patients
(Average duration since implant—96 weeks)
Dead .. .. 5 Patients
(Average duration of life—50 weeks)

Although adjacent structures were damaged, complete necrosis of the pituitary was not found in any of the cases examined *post mortem*. Sources of gamma radiation would thus seem to be unsatisfactory. However, a radioactive isotope emitting only beta particles holds greater promise. The experimental work of Rasmussen and his associates (1953) with the isotope of yttrium, yttrium90, and its safe introduction at craniotomy into the human pituitary (Yuhl *et al.*, 1955; Evans, 1957), suggested that it might prove suitable for insertion by our technique. Yttrium90 has a short half-life of 64 hours (A.E.R.E. Cat., 1957), and emits only beta particles of high energy (2·2 MeV) which have a maximum tissue range of only 1·1 cm. (Siegel *et al.*, 1956) although owing to the rapid fall-off of the beta radiation the effective range is considerably less. The target substance, yttrium oxide (Y_2O_3) is a powder which can be compressed into rods, which when heated to 1,700° C. fuse into a ceramic mass. We use rods of 50 mg. weight (6·3×2·3 mm.), which are activated in the atomic pile to 5–6 mc. To obtain a good distribution of radiation within the pituitary, we have modified our director apparatus to allow the simultaneous insertion of two cannulas, one through each nostril. One rod is introduced through each cannula so that they lie symmetrically, one on either side of the mid-line.

[A film was shown to demonstrate the method of preparing the yttrium rods, and the

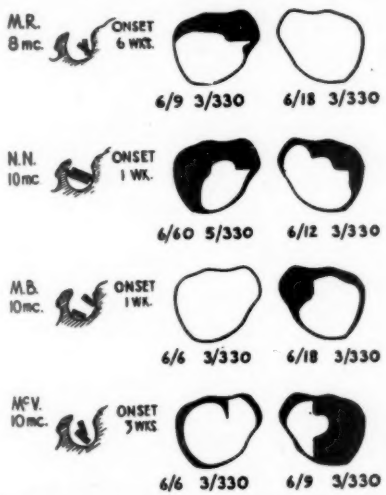


FIG. 1.—Visual damage in 4 patients following pituitary yttrium90 implantation. Visual fields and corresponding position of yttrium rods are shown for each patient.

Yttrium90.—March 1956 to February 1957: Total No. of cases 34. No. with visual defect 4.

technique of their implantation: "The Treatment of Advanced Breast Cancer. A Technique for the Implantation of Radioactive Yttrium into the Pituitary Fossa."]

Since March 1956, 34 patients with breast cancer have been treated by yttrium implantation of the pituitary. All patients have been in an advanced stage of their disease with multiple and widespread metastases, and were referred to us for treatment only when the radiotherapists considered that other forms of therapy offered no hope of palliation. One patient with massive pulmonary metastases died under anæsthesia. 4 patients developed visual defects (Fig. 1), but these did not progress and caused only slight disability. While temporary polyuria may occur during the first few weeks after implantation, only two patients have had permanent diabetes insipidus (Fig. 2). One of these had a visual defect, and in both the rods were placed in the upper part of the fossa. In 4 patients, profuse rhinorrhœa commenced 4 to 27 days after implantation. 3 patients were treated by muscle graft at craniotomy (Mr. J. Sloan Robertson), while in the fourth rhinorrhœa ceased, following an attack of meningitis. A post-mortem finding which might have predisposed to rhinorrhœa was a fracture of the sella turcica, doubtless caused by the forcible insertion of the trocar in two places. We now use a diamond steel drill to cut a clean hole in the bone. A guiding sheath is first introduced until its end strikes the outside wall of the pituitary fossa.

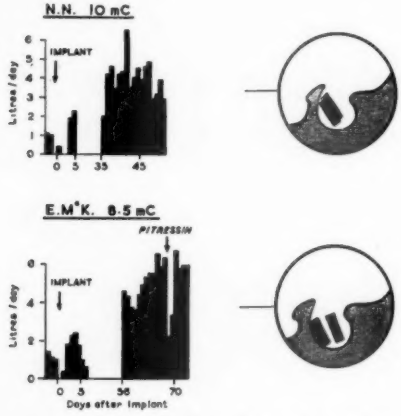


FIG. 2.—Urine volumes before and after implantation of the pituitary with yttrium90 in two patients with permanent diabetes insipidus. The position of the yttrium90 rods is also shown. Treated to February 1957: 34 patients. Severe permanent diabetes insipidus: 2 patients.

Through this sheath the cutting tool is inserted to bore a hole in the bone which allows the seed-introducing cannula, but not the guiding sheath, to enter the pituitary fossa. The length of this cannula is such that it will project only three-eighths of an inch beyond the guiding sheath, so that accidental over-penetration cannot occur (Fig. 3).

Post-mortem examination has been carried out on 7 patients at variable times after implantation. In 2, the gland was completely destroyed (Fig. 4) and neither of these had a visual defect, while in a third only a few cells remained in one lobe. The estimated extent of necrosis in the others was 90–95% of the gland mass.

None of 4 patients who had previously failed to respond to adrenalectomy had any improvement following implantation. In an acromegalic with breast cancer, the large size of the pituitary fossa necessitated an increase of the dose of yttrium to 18 mc.

Our endocrine survey of these patients includes estimates of pituitary (gonadotrophins), adrenal and ovarian (total 17-ketosteroids and their fractions[1], oestrogens and uropepsin) and thyroid (I^{131} uptake and serum cholesterol) functions. The effect of withdrawing cortisone maintenance therapy on the clinical state and steroid excretion is also determined. It would appear that the patient may benefit initially despite incomplete destruction of the gland. That later relapse may be associated with recovery of gland function was suggested by the clinical course of 2 patients who initially responded but relapsed nine and eleven months after radon implantation. At the time of their relapse there was evidence of returned pituitary function and both patients had a further remission when the adrenals were removed (Fig. 5, one case).

[1]Estimated by Dr. Ronald Hobkirk, B.E.C.C. Fellow.

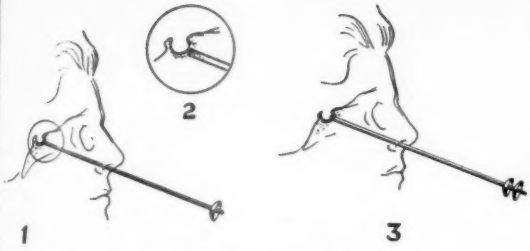


FIG. 3.—Method of cutting hole in the sella turcica to prevent fracturing of bone. (1) Guiding sheath inserted. (2) Drill penetrating sella turcica. (3) Cannula introduced through guiding sheath and drill hole.



FIG. 4.—Transverse section of pituitary thirty-four days after implantation of 11·3 mc. yttrium90 in two rods. Destruction is complete.

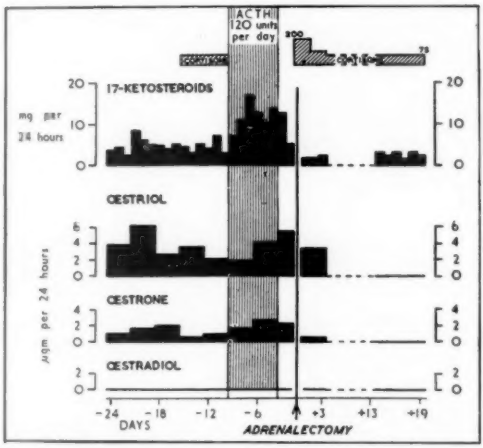


FIG. 5.—Urinary excretions of œstrogens and 17-ketosteroids in a female with breast cancer before and after removal of the second adrenal gland, the ovaries and one adrenal having been previously removed. Pituitary radon implantation had been carried out nine months previously with initial response followed by relapse. Further regression followed adrenalectomy.

Our aim is to develop a simple method of destroying the pituitary safely and completely. Until this is achieved, pituitary implantation should not be regarded as a satisfactory alternative either for adrenalectomy or for surgical hypophysectomy, except in the debilitated patient.

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Mr. E. J. Radley-Smith (Royal Free Hospital):

The indications for hypophysectomy are: widespread cancer of the breast, cancer of the prostate and possibly malignant melanoma after it has been disseminated. The indication of carcinoma of the breast is well-agreed. Although some centres do not report good results in carcinoma of the prostate, I have found that it does respond in some cases excellently. The world literature on hypophysectomy for malignant melanoma is very scanty and unfavourable but in view of the difference between my own findings and those of others on carcinoma of the prostate, it is perhaps justifiable to gain further experience by applying this operation to malignant melanoma.

The methods of destruction of the pituitary gland are numerous and I personally combine as complete a surgical removal as is possible with the subsequent insertion of unscreened radio-active gold.

I agree with Mr. Murray Falconer that the pituitary can be removed surgically by retracting the frontal lobe and sucking out the basal cisterns, and I have not found it necessary to institute drainage of the ventricles or the lumbar sac. While I agree with him that retraction of the frontal lobe does give good access—and I did this in at least the first 50 cases—I am now considering that it should be replaced by partial resection of the right frontal pole. Retraction of the frontal lobe, particularly when some of the superior cerebral veins have to be coagulated, may lead to hæmorrhage into the substance of the frontal lobe especially if some unsuspected metastases are present in the lobe. This is a point in favour of resection of the frontal pole and part of the frontal lobe. Anosmia is distressingly frequent although the operation is on one side only and retracting and stretching of the olfactory apparatus must be a factor. I have tried section of the pituitary stalk only in one case, and a favourable response was obtained. When relapse occurred some months later, the pituitary gland was surgically removed. No new connection between stalk and gland had been established; histology showed that there was much surviving tissue in the gland which had been cut off from the stalk for several months.

Whereas in the Guy's-Maudsley Unit an attempt has been made to compare the benefits of hypophysectomy with those of adrenalectomy, at the Royal Free Hospital we have approached this matter from a totally different angle. While we have endeavoured to confer benefit on the patients by this operation, we have also used it as a method of learning more about the physiology of the pituitary gland and the biochemical control of patients after its removal. I am glad to acknowledge the extremely generous help from the British Empire Cancer Campaign which has enabled us to employ full-time research workers in this subject.

Patients after hypophysectomy are, I think, a good deal more easily managed and in less danger than after adrenalectomy. Indeed, one of my patients after hypophysectomy withstood a laminectomy without any more effect than would have been produced in a normal person. Another returned to hospital many months later for the removal of an acute appendix and at that operation one was able to observe the regression of the enlarged liver and its secondaries which had caused jaundice at the time of the removal of the pituitary. I agree with Mr. Falconer that the extreme diuresis following operation generally subsides.

With regard to results, in the early work on this subject cases, however unfavourable, were subjected to operation and this accounts for some of the early deaths after operation. Of those patients who survived operation for more than three months, 84% showed subjective improvement and 56% objective improvement. Although in some series subjective improvement is not even considered, I feel that it should not be ignored. In many, the pain from bone secondaries was abolished immediately after operation, although they later succumbed without X-ray evidence of recalcification of the secondary deposits. This relief from severe pain is worthy of comment.

Among the 56% who have improved objectively there has been the disappearance of jaundice, the return of a very large liver to normal and the disappearance of skin secondaries both near and distant from the primary growth. Malignant effusions in the peritoneal, pleural and pericardial cavities are not always abolished at once, if at all, but the intervals between aspirations which may have been as short as ten days before operation may be as long as three months afterwards. In a few cases serial biopsies have shown histological evidence of regression.

It is clear that we still know next to nothing about the results of this operation, but the results in the first 60 have been more than sufficiently encouraging to suggest that the work should continue. We are still hoping that the investigations will one day enable us to tell which cases will respond well to the operation and which will not. At the moment we merely have some indications of those who are going to respond well but we are disinclined to reject any case with the exception of the moribund. The use of hypothermia has made the operation much easier and has given the patients a much calmer convalescence.

Mr. W. P. Greening (Royal Marsden Hospital):

The purpose of this paper is to discuss the effect of beta radiation, using yttrium90, on the human hypophysis; and to show whether the transphenoidal insertion of yttrium90 rods, in an attempt to destroy the pituitary gland, is either a justifiable or worthwhile procedure.

We think that interstitial irradiation of the pituitary has a definite place in the treatment of selected cases. It is not a substitute for ablative surgery but an alternative procedure for those patients where a high operative mortality is expected, if they are subjected to a major operation.

Complete destruction of the gland is desirable but not essential, and worthwhile remissions may be obtained, with relief of symptoms, when a large part is destroyed.

Since metastatic cancer of the breast inevitably terminates in death, it would be as well to review the different methods of treatment at present available.

Galton, in 1950, published a report dealing with 70 cases of breast cancer treated by androgens. All his patients were in an advanced stage of the disease and were completely unselected.

He reported a failure rate of 50%, a success rate, described as successful or moderately successful, giving a combined total of over 40%. He said that of the 30 patients deriving benefit from the treatment, 21 obtained a remission lasting six months or more, 10 over one year and 3 over eighteen months. His maximum success rate was between the ages of 45 and 50, but a similar, though smaller, peak occurred between the ages of 35 and 40.

Improvement following œstrogen therapy in the post-menopausal patients is of a similar order.

Cade, in 1954, in an assessment of the results of adrenalectomy in a series of 36 patients, gave a complete absence of response in 29%, a very successful rate of 23% and a less successful, though still improved, rate of 31%. He gives an extended survival of up to twenty months, and remarks that successful results were achieved in about 52% of the patients.

The results of hypophysectomy as reported by Luft (Olivecrona and Luft, 1957), Pearson *et al.* (1956) and Kennedy (1956) show a slight increase in the success rate and a mortality corresponding favourably with that of adrenalectomy. However, in Luft's series hypophysectomy was achieved in only a few cases, and there has been a considerable improvement in his recent results, due to complete removal of the gland. The series reported by Kennedy was carefully selected, and this may account for the high rate of remission.

This remarkable uniformity of results obtained by varying methods of treatment, indicates that hormone responsiveness in breast cancer is limited to half of the patients.

Only 5 women out of 10 will benefit from *any* method which alters the endocrine balance.

These facts make it necessary to balance the magnitude of the treatment against the result that may reasonably be expected.

A mortality of 6% in both adrenalectomy and hypophysectomy, and a morbidity rate in the latter operation of similar proportions is inevitable. In both operations adrenal rests and ectopic hypophyseal tissue may be present in a significant number of cases. Any minor procedure, therefore, tolerated with ease by the patient and accompanied by a low mortality and morbidity, must be worth considering.

It seemed that a small group of patients with metastatic breast cancer who, because of their poor general condition were considered unsuitable for ablative surgery, might benefit from interstitial irradiation of the pituitary, and we were, in the first place, trying to devise a method of either completely or almost completely destroying the gland, without the hazards or inconvenience of a major operation.

50 patients, unsuitable or unfit for adrenalectomy, and possibly therefore for surgical hypophysectomy, were treated by interstitial irradiation of the pituitary using unscreened radio-active gold. As this form of treatment was regarded only as temporary palliation, every effort was made to avoid complications caused by damage to the neighbouring structures, and to select carefully the patients who might be hormone responsive.

The activity of the gold seeds used in these cases was increased from a low value at first up to 20 mc. towards the end of the series. The destruction of the gland was inadequate but the complications were few. They were damage to the parasellar nerves in 3 cases, two VI nerve and one III nerve palsy. There was one case of cerebrospinal rhinorrhœa.

The success rate and duration of the remission so produced was not considered good enough to justify continuing on these lines. For the last 30 cases we have used yttrium90, because it is a pure beta emitter and has a short half-life of 64 hr. The yttrium90 rods used are made of sintered yttrium oxide, and are 1·3 mm. diameter, and 4·0 mm. long. Each source has an activity of approximately 3 mc. at the time of implantation.

Investigations by a combination of film and ionization chamber techniques show that along the perpendicular axis, the half-value layer of tissue is 0·7 mm. It has also been shown that with an activity of 3 mc. the total dose is approximately 70,000 rad at 3 mm. from the rod; the necrotic boundary has been found to lie at this distance in a number of post-mortem sections of the hypophysis, and is a spherical volume of complete necrosis surrounded by normal tissue. The boundary transition between normal and necrotic tissue is extremely narrow.

In this series a success rate of 40% has been obtained, a figure not dissimilar to those produced by endocrine therapy and ablative surgery, although it is already apparent that the length of the remission is probably shorter.

The immediate operative mortality has been 3%, but few of these cases would have been even remotely considered fit for adrenalectomy.

One patient developed cerebrospinal rhinorrhœa and one died of meningitis eight weeks after operation. There was no apparent cause for this at post-mortem, the floor of the sella was intact and the pituitary almost completely destroyed. There are two unilateral III nerve palsies in this series, and one unilateral optic atrophy. The urinary gonadotrophin in the cases treated by yttrium90 is estimated before, and at monthly intervals after, the operation, using the method developed in the Clinical Endocrinology Research Unit in the University of Edinburgh, and we are indebted to Dr. L. A. Loraine and Professor Boyland for help and advice with these estimations.

The biological assay is based on the method of Klinefelter, Albright and Griswold, 1943, depending on the enlargement of the uterus of intact immature mice, 20–22 days old weighing 8–10 grams.

We find that 80% of cases show that gonadotrophin is completely eliminated from the urine post-operatively, in amounts detectable by this bio-assay.

In considering the technique of implanting the yttrium, the following criteria must be satisfied:

(1) There must be accurate insertion into the hypophysis.

(2) The dose must be sufficient to cause necrosis of the gland but not to affect the surrounding structures.

(3) It should be capable of being done quickly and easily without damage to the floor of the sella turcica.

(4) Unless these conditions are completely satisfied the operation should not be undertaken.

We use an image intensifier working in two planes. In the lateral view there is no difficulty but we find that a modified Townes' view in the antero-posterior projection is of great value in locating the sella.

Following the operation, in most cases little discomfort is experienced, but in some, aspirin or codeine is necessary to relieve headaches for the first few post-operative days.

The patient is kept on antibiotic cover both before and after the procedure.

Cortisone is withheld until there are signs of adrenal insufficiency. They appear at about the seventh day and are loss of appetite, nausea and vomiting. They cease as soon as cortisone is administered.

Transient diabetes insipidus occurs in most cases between the second and third weeks.

We think that damage to the chiasma or surrounding structures can be completely eliminated by accurate placing of the rods under fluoroscopic control.

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Section of Urology

President—CUTHBERT E. DUKES, O.B.E., M.D., M.Sc., F.R.C.S.

[*February* 28, 1957]

DISCUSSION ON MODERN TRENDS IN THE TREATMENT OF GENITO-URINARY TUBERCULOSIS

Mr. Walter M. Borthwick:

Chemotherapy in Urinary Tuberculosis

INTRODUCTION

In 1948 a controlled trial was started in Robroyston Hospital into the value of three months' streptomycin in urinary tuberculosis. The preliminary results were given by Jacobs and myself (1950). Later, Wimsett (1952) added to these results by considering the value of three months' streptomycin and PAS. In these two communications 137 patients were considered. Briefly, the conclusions reached were that streptomycin had little or no effect on an established destructive renal lesion; in a few patients there was a possibility that the focus may become shut off although reactivation was always a possibility. Streptomycin therapy could not therefore be recommended to supplant surgery but these drugs, streptomycin alone or streptomycin with PAS, had a definite beneficial effect on secondary cystitis although streptomycin appeared to accelerate or even produce vesical contracture in some cases.

Later isoniazid became available and initially we, like many others, made the mistake of using it alone in a number of cases. Results which at first appeared promising were not maintained, and bacterial resistance developed in a high percentage of cases and in some of these the renal lesion became very vascular and the local progress of the disease alarming. With the realization that none of these drugs should be used singly came a definite planned programme, sponsored by the Research Committee of the Tuberculosis Society of Scotland, into the effects of the various combinations of streptomycin and PAS, streptomycin and isoniazid, and PAS and isoniazid in urinary tuberculosis. Eighteen months ago a fourth group was added using all three drugs.

Initially streptomycin was given for three months but we soon learned that treatment for that length of time was insufficient; we now carry it on for at least nine months and often eighteen to twenty-four months depending on the state of the disease.

TABLE I

Group 1: Unilateral renal tuberculosis; minor lesion without cystitis.

Group 2: Unilateral renal tuberculosis; major lesion necessitating nephrectomy; cystitis.

Group 3: Bilateral renal tuberculosis; nephrectomy for the more advanced lesion.

Group 4: Tuberculosis occurring in the remaining kidney subsequent to nephrectomy for unilateral disease.

Group 5: (*a*) Major bilateral tuberculous lesions; (*b*) Minor bilateral tuberculous lesions.

The grouping of the patients (Table I) followed the lines adopted by Jacobs and myself in 1950, but comparable tables of results cannot be produced where more than one combination was used in succession. Further, we have no experience on the suggested alternating regime of Ross and his colleagues (1951). It is, however, to be welcomed that different centres use different regimes so that soon we may be able to decide on the best method of attack.

TABLE II.—CHEMOTHERAPY USED IN 218 PATIENTS WITH URINARY TUBERCULOSIS

Chemotherapy	Group 1	Group 2	Group 3	Group 4	Group 5	Total
S+P	17	45	8	6	10	86
S+H	7	23	2	5	7	44
P+H	9	40	10	3	8	70
S+P+H	5	10	3	0	0	18
Total	38	118	23	14	25	218

S=Streptomycin. P=PAS. H=Isoniazid.

The results to be given concern 218 patients who had one of the four basic forms of treatment (Table II). 86 patients received streptomycin and PAS; 44 received streptomycin and isoniazid; 70 received PAS and isoniazid, and 18 the three drugs.

Patients were allocated by random selection by an independent non-medical person. Each patient after complete urological examination and definite proof of the existence of urinary tuberculosis, was placed in one of the categories. The dosage used was 1 gram of streptomycin, 10 grams of PAS and 200 mg. isoniazid daily, including Sundays.

Group 1.—In Group 1 there were 38 patients, 17 of whom received streptomycin and PAS, 7 streptomycin and isoniazid, 9 PAS and isoniazid and 5 streptomycin, PAS and isoniazid.

The lesion in the affected kidney was demonstrable by pyelography in every case and in 12 instances it consisted of a localized cavity from 2 to 5 mm. in diameter. After chemotherapy there was conversion of urine in 33 of the 38 patients. 7 of the 33 patients in whom there was urinary conversion were in the group with definite cavitation and in every case the lesion was unchanged to any marked degree. Partial nephrectomy was carried out in 2 of these 7 and the remaining 5 have been under observation up to four years without showing a relapse. Histological examination of the resected specimens after partial nephrectomy did not show any active tuberculosis.

5 patients in the definite cavity group did not show conversion and nephrectomy was carried out. All 5 had cavities approaching 5 mm. and histological examination showed active disease without any bacterial resistance in 4 but in 1 the organisms were resistant to streptomycin. In none did the disease spread to the bladder or contralateral kidney.

In the isolated renal lesion without cystitis it seems reasonable to give a combination of drugs. We would advise the cessation of therapy for seven to ten days after three months, for check-up examination. Even without conversion at this stage chemotherapy should be carried on for a further three months before re-examination. Resistance tests are necessary but non-conversion at six months with drug-sensitive organisms, usually, in our experience, necessitates surgical intervention which may be limited in its extent. The majority will, however, convert to a negative urine but it is unlikely that definite pyelographic abnormalities will show much alteration. In these the treatment should be carried on for at least eighteen months. Under adequate chemotherapy protection of the bladder and the contralateral kidney seems adequate.

There was nothing to choose between the various combinations in the results.

Group 2.—In this Group there were 118 patients forming the largest group and the type most frequently seen in practice. 45 were treated with streptomycin and PAS; 23 streptomycin and isoniazid; 40 PAS and isoniazid, and 10 all three drugs. All suffered from cystitis. At the end of treatment there was conversion in all and in none was there spread to the contralateral kidney.

In every case at the first examination it was considered that nephrectomy would be necessary and in the days before streptomycin this would have been carried out. The same routine was adopted. After three months re-examination was performed and the case reviewed. Nephrectomy was considered necessary in patients with positive urines where there were: (1) ulcero-cavernous lesions in all calyces; (2) a pyonephrotic kidney; and (3) an apparently non-excreting kidney.

In 7 patients, however, partial nephrectomy was substituted for total removal of the organ, and in 10 no operation was considered necessary. In these 10 there was conversion of the urine and the pyelographic appearances had shown marked alteration. In the initial examination it was thought that the disease affected all areas of the kidney, producing marked hydrocalicosis and marked hydronephrosis. This was probably due to kinking and œdema and it shows the value of an initial period of three months' chemotherapy before a definitive decision is made.

With regard to the renal lesion there was no difference between the four combinations but the effect on cystitis will be considered later.

In the 10 where no operation was necessary and in the partial nephrectomy cases, chemotherapy was continued for at least eighteen months. In the others the duration of treatment was nine to twelve months depending on bladder response.

Group 3.—There were 23 patients in this Group: 8 received streptomycin and PAS; 2 streptomycin and isoniazid; 10 PAS and isoniazid and 3 streptomycin, PAS and isoniazid. On initial examination all had a marked lesion on one side necessitating nephrectomy and a smaller lesion on the other. After three months' chemotherapy 22 of the 23 had nephrectomy. In one instance marked pyelographic changes had again occurred and no operation has so far been necessary for the observation period of almost two years.

The size of the lesion in the remaining kidney was small in 16 and moderate in 7 instances. In 5 deviation of the urine was necessary and follow-up has been difficult. In the remaining 18 patients there was conversion in all but 2 where partial nephrectomy was necessary

There were 5 patients who have been followed up for one to four years in whom there is a definite pyelographic abnormality although with urinary conversion.

Group 4.—This group consisted of 14 patients, 6 of whom received streptomycin and PAS; 5 streptomycin and isoniazid and 3 PAS and isoniazid.

The kidney lesions were small in 6 and definite in 8 patients. In 2 of the latter group there was complete occlusion of the lesion (1 with streptomycin and PAS and 1 with streptomycin and isoniazid) and these lesions have remained shut off for almost three years. In 7 other patients the kidney lesion at the end of treatment was unchanged but the urine free of tubercle bacilli in all but one. In this last patient a partial nephrectomy produced conversion.

Group 5.—25 patients were placed in this Group, 10 of whom received streptomycin and PAS; 7 streptomycin and isoniazid and 8 PAS and isoniazid. After treatment there were 13 patients with advanced kidney lesions unchanged from the first examination. The urine was positive in 7. In 6 others a moderate lesion on one side improved so that nephrectomy of the contralateral kidney was carried out with good result. An additional patient had a moderate lesion which improved and became suitable for partial nephrectomy and in one other instance a nephrectomy on one side and partial nephrectomy on the other were successful.

From these findings in renal disease it would appear that all four combinations are effective when used for a period of at least nine months. It seems unlikely that an established destructive lesion of the kidney will disappear but in certain cases a lesion may become shut off and the best drug to achieve this would appear to be streptomycin.

TABLE III.—EFFECT OF CHEMOTHERAPY ON CYSTITIS IN 161 PATIENTS

Group	No.	Slight cystitis to normal mucosa				Moderate cystitis to normal mucosa				Severe cystitis to normal mucosa			
		SP	SH	PH	SPH	SP	SH	PH	SPH	SP	SH	PH	SPH
2	110	18	7	16	5	13	7	16	4	8 (6)	7 (3)	8 (2)	1
3	17	3	1	5	0	2	0	4	1	0	0	0	1 (1)
4	13	2	2	1	0	3	1	2	0	1	1	0	0
5	21	6	2	2	0	1	2	2	0	1	1	4 (1)	0
Total	161	29	12	24	5	19	10	24	5	10	9	12	2

S=Streptomycin. H=Isoniazid. P=PAS

Figures in parenthesis represent diminished bladder capacity.

TABLE IV.—EFFECT OF CHEMOTHERAPY ON CYSTITIS IN 19 PATIENTS

Group	No.	Severe cystitis to severe bladder contracture			
		SP	SH	PH	SPH
2	8	6	2	0	0
3	6	3	1	1	1
4	1	0	1	0	0
5	4	2	2	0	0
Total	19	11	6	1	1

S=Streptomycin. P=PAS. H=Isoniazid.

TABLE V.—EFFECT OF CHEMOTHERAPY ON 52 PATIENTS WITH SEVERE CYSTITIS

Chemotherapy	No.	Normal mucosa and capacity after treatment	Normal mucosa with diminished capacity	Severe bladder contracture
SP	21	4	6	11
SH	15	6	3	6
PH	13	9	3	1
SPH	3	1	1	1
Streptomycin:	39 patients:	Diminished capacity:	10 patients.	
		Severe contracture:	18 patients.	
Isoniazid:	13 patients:	Diminished capacity:	3 patients.	
		Severe contracture:	1 patient.	

S=Streptomycin. P=PAS. H=Isoniazid.

Effect of chemotherapy on cystitis (Tables III and IV).—There is no doubt regarding the efficacy of chemotherapy on secondary cystitis. All combinations gave good results.

In a patient with slight or moderate cystitis one can expect return to normal with adequate treatment. Even with severe cystitis return to normal is possible but diminished bladder capacity or severe bladder contracture are more likely.

Table V : In 52 patients who had severe cystitis 20 returned to normal; 13 had diminished capacity of the bladder and 19 had severe bladder contracture. 39 received a combination containing streptomycin and 10 of these had a diminished bladder capacity and 18 severe bladder contracture; 13 had a combination which did not include streptomycin, 3 of these had diminished bladder capacity and 1 severe bladder contracture. There seems little doubt that contracture is more likely with streptomycin.

The choice of combination in the treatment of urinary tuberculosis should depend mainly on two things: (1) A knowledge of what each combination will do for tuberculous lesions in general; and (2) Appraisement of the type of lesion in a particular case. This may require reviewing after treatment for three to six months.

Dick (1953 and 1954) has examined all our resected specimens and reported on them without knowing what treatment the patient received; his opinions were later compared with the clinical data.

Streptomycin and PAS.—Dick found that streptomycin and PAS caused rapid cessation of activity in spreading lesions which then fibrosed. In small lesions, slight caseation in the centre may be absorbed but more often caseation occurs in larger areas and here the fibrosis of streptomycin therapy traverses this area and aids the development of hyalinized areas. In active cavity walls, fibrosis occurs and frequently the result of six to nine months' chemotherapy is a smooth-walled dense fibrous cavity, a result which according to Dick was relatively infrequent before chemotherapy. One serious drawback is that by the time renal tuberculosis is diagnosed the lesions may have been present for a considerable time and are not active. Streptomycin and PAS appear to have little effect on this type of lesion.

PAS and Isoniazid.—Adequate dosage of PAS and isoniazid appears to produce almost immediate cessation of activity in spreading lesions. The active lesion is now converted into a resolving one with increased vascularity and small hæmorrhages, removal of dead tissue and caseation and an active regeneration in the neighbourhood. Small tubercles may disappear leaving only a focus of very loose fibrous tissue and a recent lesion in a calyx or small cavity wall can be completely repaired, leaving only a slightly dilated calyx. Inactive lesions are not affected.

Streptomycin and Isoniazid.—Early on the isoniazid effect is predominant. After three months, resolution of active lesions has occurred and it is not possible to distinguish between the effect produced by streptomycin on the one hand and isoniazid on the other.

The choice of drugs to be used in urinary tuberculosis can thus be summarized:

(1) If the organism is known to be resistant, or becomes resistant to any of the drugs, the other two will be used.

(2) If there is moderate to severe cystitis, with or without ureteritis, avoid the use of a combination containing streptomycin thus, as far as possible, preventing contracture.

(3) If it is desired to close off a cavity with a narrow neck, use a combination with streptomycin.

(4) It is not advisable to give daily streptomycin for nine to eighteeen months in view of toxic manifestations, of which we have seen many, particularly in the older age groups.

(5) In the presence of secondary infection it should be remembered that PAS and isoniazid are not effective against pathogens, so that streptomycin or some other antibiotic should be used.

(6) In hospital it is very much easier to give streptomycin than at home and when the patient leaves hospital a combination of PAS and isoniazid is more suitable particularly for work and normal life.

(7) When PAS and isoniazid are being given, it is advisable to give them in a combined form so that the patient in fact takes both.

(8) Dosage: PAS 10 grams; isoniazid 200 mg.; streptomycin 1 gram daily. This last is better than prescribing streptomycin three times a week.

(9) The duration of chemotherapy should be at least nine months and often as long as twenty-four months.

(10) Drugs should be stopped for seven to ten days prior to an examination.

(11) Specimens for culture should be despatched to the laboratory for examination as soon as possible after collection.

Finally, a persistent positive urine may be due to drug-resistant organisms or the presence of small areas of calcification nestling in the apex of a cavity imprisoning colonies of organisms. A pyelographic abnormality does not necessarily indicate active disease when

the urine is free of acid- and alcohol-fast bacilli. Some "cavitated lesions" have been observed up to five years after cessation of treatment without any reactivation.

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Dr. William G. Wimsett:

Cases Illustrating Effects of Chemotherapy in Urinary Tuberculosis

The following cases treated at Robroyston Hospital, Glasgow, have been selected to illustrate certain aspects of the treatment of urinary tuberculosis.

Case I.—M. A., female, aged 24.

Streptomycin was given, it being the only drug in use in 1950. Prior to treatment the bladder urine contained tubercle bacilli; capacity 14 oz.; a small tuberculous ulcer was present between the ureteric orifices. After three weeks of streptomycin 1 gram daily a routine investigation by an E.N.T. surgeon revealed slight vestibular damage. The significance of this finding not being fully appreciated the drug was continued for a further nine weeks being then withdrawn following a complaint of impaired hearing. A further examination revealed cochlear nerve damage. Study of the frequency chart showed an increase of frequency starting three weeks after the commencement of streptomycin and gradually worsening.

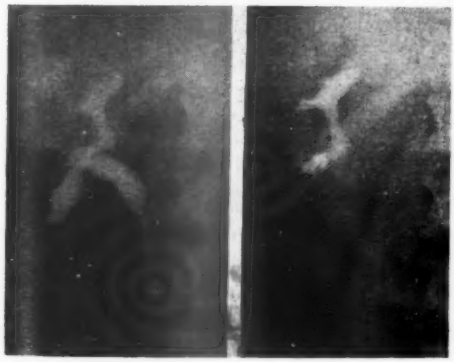
Conversion of the urine in this case had been obtained at the expense of the vestibular, cochlear and bladder function.

The pyelo-ureterogram obtained as a result of regurgitation of the radiopaque fluid from the bladder showed moderate dilatation due to back pressure, the kidney being unaffected. Ureterocolic anastomosis was subsequently performed by the Nesbit technique then in vogue.

Now in her seventh post-operative year she remains well and in employment.

Case II.—R. S., male, aged 23.

Following a left nephro-ureterectomy in May 1949 this patient was referred to Robroyston Hospital with a persistently positive urine.



Before After

FIG. 1 (*Case II*).

Investigation showed disease of the solitary right kidney involving the lower and middle groups of calyces (Fig. 1). Urine samples from bladder and right kidney contained tubercle bacilli, unassociated with secondary cystitis. Streptomycin was given with PAS for a period of six months: at the completion of this treatment pyelographic improvement was noted, the diseased areas having become shut off, but the bladder urine still contained tubercle bacilli. The patient was then discharged and maintained on daily PAS with isoniazid. Three-monthly investigations were performed during this period. After twelve months urine conversion resulted; chemotherapy was maintained a further six months.

Six years later the bladder and solitary kidney urines remained negative and pyelographic studies show that the lesions remain shut off.

Case III.—J. S., male, aged 24.

On admission intravenous pyelogram showed hydronephrosis of the left kidney with a large filling defect present at the upper group of calyces. There was a slight cystitis and the urine contained tubercle bacilli. From the pyelographic appearances at this stage it was considered that nephrectomy would be necessary. The case was placed in Group 2 and following our customary procedure a course of chemotherapy was given for three months.

Streptomycin and isoniazid were given and at three months the urine was free from tubercle bacilli; the bladder was normal and pyelographic improvement was noted. It was therefore decided to continue chemotherapy rather than to operate. This chemotherapy was continued for a further three months, the patient after routine investigation being discharged on maintenance PAS and isoniazid for a further six months.

Two years after completion of chemotherapy the urine conversion and pyelographic improvement has been maintained.

Case IV.—J. H., female, aged 31.

Prior to treatment was found to have tubercle bacilli in the urine from the bladder and right kidney. A slight degree of cystitis was present. An ascending pyelogram showed disease of the

right kidney associated with the middle group of calyces. Streptomycin with PAS was given. After three months conversion of the urine took place, the pyelographic appearances were unchanged, the lesion persisting, and the bladder was normal.

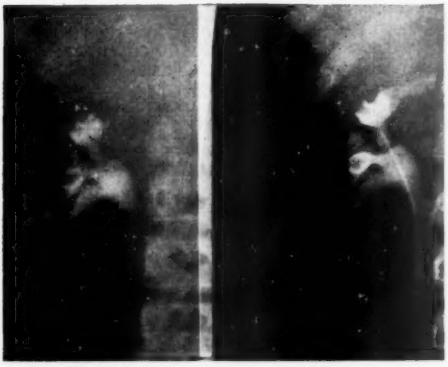
Streptomycin with PAS was continued for a further three months, the urine conversion being maintained, the patient was discharged and had a maintenance course of PAS and isoniazid for a further six months. To date the urine is free from tubercle bacilli though the filling defect persists.

Case V.—H. G., male, aged 25.

Patient was admitted with a tuberculous epididymitis but with no urinary symptoms, and was found to have irregular filling defects involving the upper calyces of the right kidney. Tubercle bacilli were cultured from both bladder and right kidney urines; there was no cystitis.

PAS and isoniazid were given and three months later no tubercle bacilli were recovered and pyelographic improvement was noted. A further three months' PAS and isoniazid were given, the patient being discharged on chemotherapy to complete twelve months' treatment.

Eighteen months after cessation of treatment the urinary conversion and pyelographic improvement have been maintained.



Before After

FIG. 2 (*Case VI*).

Case VI.—M. R., female, aged 14.

In this case a small irregular filling defect was exhibited at the lower pole of the right kidney (Fig. 2). Urine from the bladder and right kidney contained tubercle bacilli. The bladder mucosa was normal.

Streptomycin and isoniazid were given and three months later the urine was found to be negative, the filling defect persisted but its wall appeared smoother. After six months' chemotherapy the patient was discharged and received maintenance chemotherapy for a further six months.

Three years later the urine remains free from tubercle bacilli but the filling defect in the right kidney persists.

Case VII.—A. McC., male, aged 27.

Early in 1950 this patient was found to have a minimal lesion involving the right kidney, there being no cystitis.

Following a three months' course of streptomycin with PAS the urine was free from bacilli though the pyelographic lesion persisted (Fig. 3A).



FIG. 3A (*Case VII*).—After three months' treatment.



FIG. 3B (*Case VII*).—Four years later. No drugs; no supervision.

The need for maintenance therapy was not appreciated at that time and the patient was dismissed to attend for three-monthly examinations.

Unfortunately he left the city and we were unable to trace him. Four years later he was admitted in a profoundly toxic state with advanced disease of the right kidney, ureter and bladder (Fig. 3B).

The urine from both kidneys and the bladder contained tubercle bacilli.

PAS with isoniazid was given and after one month a right nephrectomy was performed. At the completion of three months' chemotherapy the urine from the bladder and solitary left kidney was free from bacilli, cystitis was improved and the bladder capacity had increased from 6 to 10 oz.

A full course of maintenance therapy was given and eighteen months later the improvement was maintained.

Case VIII.—J. N., male, aged 26.

Early in 1951 this patient had bilateral minimal lesions involving the upper calyces. He was given streptomycin and PAS but after two months he left hospital and had no further treatment.

Six years later he was referred as an outpatient for investigation of a troublesome frequency.

Samples of urine from both kidneys and bladder contained numerous tubercle bacilli, there was a severe cystitis and the ascending pyelogram showed advanced bilateral disease with large cavities present at all groups of calyces. The patient died soon after admission.

In conclusion I have attempted to emphasize the excellent results that can be obtained in suitable cases, particularly in localized lesions, given adequate chemotherapy.

The last two cases are of interest because they illustrate the futility of short courses of chemotherapy and the need for prolonged observation after treatment has been completed.

Mr. Arthur Jacobs (Glasgow):

The Place of Surgery in Treatment

As a consequence of chemotherapy, the place of surgery in the treatment of genito-urinary tuberculosis has become modified but has lost nothing of its former importance. This will be apparent from Table I, which lists the operations carried out for renal tuberculosis and its sequelæ, on patients from the Genito-Urinary Tuberculosis Unit at Robroyston Hospital, Glasgow, during the past three years.

TABLE I.—OPERATIONS DURING 1954, 1955 and 1956

Nephrectomy and nephro-ureterectomy ..	99	Ureterocolic anastomosis ..	8
Partial nephrectomy	7	Ileocystoplasty	7
Reimplantation of ureter	2		

Nephrectomy.—Nephrectomy is still required for advanced unilateral renal tuberculosis. Operation should be preceded by a regime of chemotherapy lasting for about three months. Occasional exceptions calling for early intervention are when a superadded pyogenic infection causes toxic symptoms or a gross pyonephrosis develops. Pyelographic changes which would formerly have been regarded as evidence of widespread disease and an indication for nephrectomy, may occasionally improve under treatment and show that surgery is not required or that a partial nephrectomy is possible. Hanley and Borthwick both consider that pyelographic appearances which alter in this way are likely to result from œdema rather than from ulcerative tuberculous foci. When a kidney has been extensively destroyed, chemotherapy will not eliminate the need for nephrectomy; nor can it be envisaged that any new agent will ever have this effect, for a cavity-ridden kidney cannot be restored. In bilateral disease, therapy has actually increased the scope for nephrectomy and may permit removal of a kidney with widespread disease while relying on the drugs to deal with a lesser lesion on the contralateral side or enable it to be extirpated by partial nephrectomy. A progressive decline in the incidence of advanced lesions can be anticipated as a result of the increasing success of eradicating tuberculosis.

With regard to the disposition of the ureter, one of normal calibre and consistence can be divided at any convenient point and the secured stump allowed to drop into the wound without fear of complication. When because of dilatation or induration, ureterectomy is advisable, this can be accomplished through a forward extension of the lumbar incision. If the pedicle is first tied off, traction on the ureter through the mobilized kidney will enable a removal of the tube down to the bladder through this approach. A solution of streptomycin is instilled into the renal space and the wound closed without drainage. Only in exceptional circumstances, such as a pyo-ureter involving the extreme lower end of the pelvic segment, need a lower abdominal incision be used in addition to a lumbar one.

Partial nephrectomy.—Partial nephrectomy has an established place for a localized focus of limited dimensions which proves resistant to chemotherapy. Chemotherapy for not less than four months is advisable before operation. The response is checked from time to time by repeated bacteriological and pyelographic examinations, a retrograde pyelogram being made at the outset and again before finally deciding on partial nephrectomy. Because the smaller renal lesions are to-day often arrested, the need for resecting them is diminishing. Removal of refractory segments may, however, avoid over-prolonged chemotherapy.

Reimplantation of the ureter into the bladder.—Reimplantation of the ureter into the bladder is indicated in the presence of an organic stricture at the lower end which is causing progressive dilatation and is not associated with a bladder contracture. The necessity for this type of intervention has been encountered in two instances only in the past three years. The technique used was analogous to Leadbetter's method of uretero-colic anastomosis, the trimmed end of the ureter being united to the bladder mucosa and the muscular coats of the bladder wall approximated over the implant. Experiences have

shown that this technique of reimplantation is satisfactory; narrowing does not occur and post-voiding retrograde cystograms have demonstrated no tendency to regurgitation.

Uretero-colic anastomosis.—The serious aftermath of bladder contracture and consequent progressive damage to the remaining kidney continues to occur in spite of chemotherapy—streptomycin may indeed aggravate it. I still regard uretero-colic anastomosis as a good way of relieving the effects of the impaired bladder capacity and of saving the kidney. Lattimer (1955) who favours cutaneous ureterostomy in the tuberculous case, recently wrote: "We have followed some 20 cases done elsewhere, where ureterosigmoidostomy was performed and a tuberculous ureter was transplanted into the bowel. All of these patients with one possible exception have died within a year." This to me is a surprising statement for my own follow-up (Jacobs, 1956) showed that, subsequent to the first transplant for tuberculosis, carried out in 1936 on a female patient who died two and a half years later from reactivation of a pulmonary lesion, out of 61 on whom the operation has been performed, 30 are still living. 20 of the 30 have passed their fifth post-operative year; 6 continue well and active after periods of ten to fourteen years. Among these longer term survivors are some who had gross hydronephrosis and hydro-ureter before operation, including several with no pyelographically demonstrable function in the remaining kidney. One patient operated on five years ago when she had a moderate dilatation of the renal pelvis and a ureter of thumb-like calibre, gave birth without incident to a healthy child six months ago.

In 53% of my series who were still tubercle positive at the time of the transplant, progressive tuberculous destruction of the solitary kidney was inevitable with some, particularly in the pre-chemotherapeutic era; but relief from unbearable frequency or total incontinence was often obtained for several years. The protection which chemotherapy combined with surgery may afford to-day is illustrated by the following case summary.

A nurse, 32 years of age, was admitted to Robroyston Hospital in 1950 suffering from bilateral renal tuberculosis. After six months' therapy a left partial nephrectomy was carried out and followed by a right nephrectomy three months later. She became tubercle negative but reverted after a further six months. In spite of prolonged hospitalization and therapy she developed an increasingly severe bladder contracture and was finally voiding at 10 to 20 minute intervals night and day. In June 1955 the ureter from the remaining portion of the solitary left kidney was transplanted to the pelvic colon. Six months later she was back at nursing and has continued at her hospital post since then.

After a successful ureterocolic anastomosis and in the absence of continued tuberculous activity, general well-being can be expected. The many satisfactory long-term results obtained, even when the remaining kidney has already suffered serious damage, leaves



FIG. 1.—Retrograde cystogram demonstrating bladder contracture with reflux and dilatation of ureter and renal pelvis. Right nephrectomy for tuberculous disease five years earlier.



FIG. 2.—Retrograde cystogram of same patient twenty-seven days after uretero-ileocystoplasty. The stump of the divided ureter is outlined but there is no reflux through the uretero-ileal anastomosis.

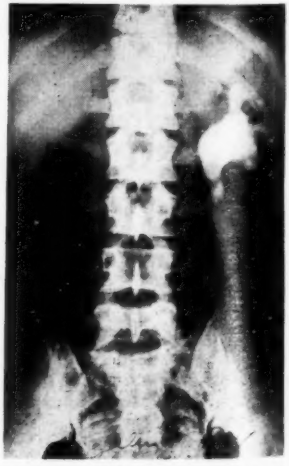


FIG. 3.—Intravenous pyelogram twenty-three days after the uretero-ileocystoplasty showing marked resolution in the pre-operative dilatation.

open to question the justification of transplanting the ureter into an isolated ileal loop as an alternative. The wet external stoma, however perfectly fashioned, is an inevitable handicap.

Ileocystoplasty.—A desirable alternative to any form of urinary diversion is a restoration of the bladder so that it can function as an adequate urinary reservoir. Ileocystoplasty or uretero-ileocystoplasty shows great promise of proving a satisfactory substitute for ureterocolic anastomosis in selected cases. I have now operated on 12 patients, 8 of whom had a tuberculous contracture. In 7 with an associated dilated ureter and demonstrable regurgitation, a closed loop of ileum was joined to the bladder and the ureter implanted into the loop (Figs. 1, 2, 3); in the remaining one, ileocystoplasty alone was done. An account of most of these cases has recently been given (Jacobs, 1956). The operation is of necessity a rather prolonged one for the ileal loop has to be isolated, the continuity of the ileum restored, the loop anastomosed to the bladder, and in the majority, the ureter isolated and anastomosed to the loop. The multiple steps of the operation, although very well borne, carry an increased liability to post-operative complications. The functional results to date are, however, proving very satisfactory. Patients who were incontinent, or nearly so, have acquired intervals of several hours between micturition. Resolution of the dilatation in the renal pelvis and ureter without continuing regurgitation has generally taken place and electrolyte disturbances are minimal. Professor Wells (1956) in his presentation on "The Use of the Intestine in Urology" collected in his survey 50 cases on whom vesical enlargement with an ileal loop had been performed for tuberculous contracture. He considered that the results were generally proving satisfactory though the duration of the follow-up, averaging twelve months, was a short one. Pyrah (1956) also considers that ileocystoplasty can be a preferable procedure to ureterocolic-anastomosis for the relief of this condition.

Conclusion.—Chemotherapy has reduced the need of surgery for small renal lesions, but has increased its scope in other directions. Definitive surgery, with less post-operative difficulties, is now possible on patients who would formerly have been unsuitable. This applies particularly to those suffering from bilateral renal tuberculosis, disease in a solitary kidney and sequelæ resulting from the infection.

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Mr. Howard G. Hanley (St. Paul's Hospital, London; Harefield Hospital) and **Dr. Raymond Parkes** (late of Harefield Hospital):

Some Observations on the Modern Treatment of Renal Tuberculosis [*Abridged*]

The following data are based upon our observations of 104 patients with renal tuberculosis treated under sanatorium conditions during the two-year period from August 1954 to August 1956.

Table I shows that 37 patients had already undergone a nephrectomy before admission

TABLE I.—104 PATIENTS WITH RENAL TUBERCULOSIS

Nephrectomy before admission to Harefield ..	37
Previous nephrectomy in bilateral disease ..	24
Total No. with bilateral disease..	55
Total No. with one kidney or bilateral disease	70

to the sanatorium. 8 of these were presumed to be unilateral lesions, but were admitted post-operatively in conformity with a modern trend in the management of this disease. Others had tuberculosis of the bladder, prostate, vesicles, or epididymides, or bone and joint or pulmonary lesions.

Routine management.—Ideally, no drug treatment was started until the diagnosis had been confirmed by culture or guinea-pig inoculation. Having established the diagnosis, we proceeded upon the assumption that the urine could be rendered tubercle free in all cases in the absence of certain complications.

These complications have proved to be, (1) obstruction or poor drainage leading to caseation and (2) of much less importance, drug resistance.

In general, if the urine can be rendered tubercle free there is no indication for surgery while under no circumstances did we consider operating until a repeat urine culture had been grown, so that at least six weeks' drug therapy preceded any surgery. In all but the most obviously destroyed kidneys we preferred to wait for three or four months.

A period of preliminary observation is essential in nearly all cases because it must be

stressed that neither the activity of the disease nor the degree of renal destruction can be assessed by one set of X-ray films.

It is not at all uncommon to find that the first excretion pyelogram shows clubbing of all of the calyces in one kidney, but that within three or four months of starting antibiotic treatment, the radiological changes have improved so much that most of the initial changes could not possibly have been due to actual tuberculous ulceration.

Our researches with the X-ray image amplifier lead us to conclude that many of these early signs of clubbing are due to mild back pressure or œdema, not ulceration, and as such are reversible.

Such a case is illustrated in Fig. 1. This woman was admitted to a hospital for removal of the right kidney shown in Fig. 1A. Fortunately for her she developed a hæmoptysis and was promptly transferred for sanatorium care. Within three months she had a sterile urine, which has remained sterile ever since. The excretion pyelogram taken five months later, Fig. 1B, shows rapid emptying of all of the calyces with no evidence of any serious cavitation. [Urine remains sterile. March 1957.]

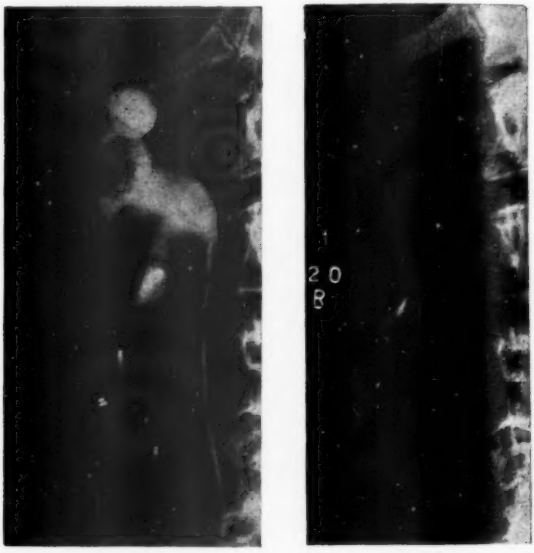


FIG. 1A. FIG. 1B.

FIG. 1.—A, Retrograde pyelogram before commencement of anti-tuberculous drug therapy. B, Excretion pyelogram five months later. Note rapid excretion of medium with no gross cavitation.

One can only repeat that any estimation of *tissue destruction* can only be based upon a series of X-rays taken over several months, while the only reliable guide to the *activity of the disease* is the absence or otherwise of tubercle bacilli in the urine.

Drug treatment.—During the period under review there was a gradual change from the Ross and Gow fortnightly courses of streptomycin and isoniazid alternating with PAS and Ethizone, to a more continuous regime of streptomycin 1 gram daily, isoniazid 400 mg. daily and PAS 17–20 grams daily given together or in pairs for prolonged periods.

No serious toxic manifestations were noted while drug resistance has not been a problem.

Only 2 of our cases proved resistant to isoniazid and this was overcome by increasing the dosage to 400 mg. daily. We now use this dose routinely and are prepared to increase it even further if necessary.

Bacteriological control.—Three consecutive early morning urines are cultured for tubercle bacilli every month whilst the patients are in hospital. Catheter specimens are taken from female patients. If any secondary infection is present sulphafurazole is prescribed for five days prior to the collection of the urines, and we have found that this reduces the percentage of contaminated Lowenstein cultures.

It is our impression at the moment that a lesion responds more satisfactorily to antibiotic therapy if some combination of the drugs is administered continuously over long periods, rather than when short two- or three-month courses are interrupted by a period of rest. We have therefore not stopped drug treatment before collecting urine specimens until two consecutive sets of monthly cultures have proved negative. Before obtaining the third set of cultures, all drugs are stopped for five days. So far, this third set of cultures has always remained sterile.

There is much controversy about the need to stop treatment before culturing urine for tubercle bacilli. It has been asserted that even small quantities of anti-tuberculous drugs in the urine will prevent the growth of tubercle bacilli on culture. If this were so, continuous drug therapy should result in negative cultures almost from the commencement of treatment. However, this has not been our experience, and we found that in spite of

a high concentration of drugs in the urine, tubercle bacilli would usually continue to grow on culture for several months after treatment was started.

Response to Drug Treatment

Reference to Table II shows that 60% of the positive cultures were converted to negative in four months and 80% in six months.

Table II.—Response to Drug Treatment

71 Patients Admitted with Positive Urine Cultures

Months	.. ..	2	3	4	5	6	7	8	9	
Conversion to negative		15	13	15	7	7	0	2	1	Total 60

43 converted to negative in 4 months = 60·5%
57 „ „ „ „ 6 „ = 80%

11 patients have remained positive:
10 for 6–8 months
1 for 22 months
of these 11, 9 are bilateral, 9 have extra-urinary lesions, 5 are over 50 years, 4 are in spinal beds or frames, 2 are paraplegic, 1 has a permanent cystotomy.

The 11 resistant cases were either in the older age groups with long-standing fibrotic disease (frequently having histories of several short courses of antibiotics in the past) or had multiple extra-urinary lesions. Tuberculous disease had been present for more than seven years in all of these 11 patients.

Apart from these truly chronic cases, the response to conservative drug therapy has been so satisfactory that surgery is never considered unless some complication occurs. We have not yet failed to sterilize the urine from a kidney unless there has been some serious degree of obstruction to drainage resulting in an area of caseation.

Indications for Surgery

Provided that the urine can be rendered tubercle free with drugs, the only indications for surgery would appear to be (*a*) to correct obstruction and promote drainage, and (*b*) to excise closed caseous areas. Tuberculosis heals by fibrosis, and this fibrosis, if occurring in certain situations, leads to obstruction which is not in the patient's best interests.

Obstruction at the neck of a calyx will lead to a pyocalyx and has been considered the chief indication for a partial nephrectomy. However, many of these closed-off calyces will eventually open up and drain into the calycine system. When this occurs we do not consider that surgery is necessary provided that the urine is tubercle free. Histological examination of such calyces after removal will show considerable evidence of healing.

Obstruction at the pelvi-ureteric junction is the most serious problem of all. During the course of treatment one has watched the "healing process" close off the pelvis slowly and inexorably although the urine may have been rendered sterile.

Obstruction at this site has been the chief indication for nephrectomy in our experience.

Obstruction at the uretero-vesical orifice calls for re-implantation of the ureter early, not when the kidney is already showing serious back pressure changes. It is vital, however, to be sure that ureteric dilatation is not due to reflux rather than a stricture. Inability to pass a ureteric catheter tells us nothing, but a micturating cystogram may be of great help. Re-implantation of the ureter is contra-indicated if the bladder is showing signs of contracture. An ileocystoplasty is a much more rational procedure in such cases.

Drug penetration in obstructed lesions.—We have noted on several occasions that streptomycin, isoniazid or PAS may not be detected in the contents of the completely closed-off pyonephrosis after removal, although the concentration of these drugs in the urine from the other kidney has been high. Also in these sealed-off kidneys one may frequently find active tubercle bacilli in the contents of the cavities in spite of prolonged treatment. It would appear that once the pelvi-ureteric junction, or even the neck of a calyx, becomes completely sealed off, the physiology is altered in that, even if excretion and reabsorption of fluid continues in the glomeruli and tubules, the amount of drug excreted into the cavities becomes very small. Coupled with the reduction of vascularity, as shown by the deposition of calcium, it is not surprising that blood-borne drugs are less effective in the presence of obstruction and caseation.

The assertion that a closed and possibly calcified non-functioning kidney was a source of danger and should be removed (Hanley, 1952) still holds good in spite of the use of anti-tuberculous drugs.

Calcification developing during the course of treatment.—Scattered areas of calcification are now appearing in several of our drug-treated and quiescent kidneys. This indicates that multiple areas of ulceration have become walled off by fibrous tissue and that calcium

has been deposited in the resultant avascular tissue. It is hoped that these areas were sterilized by drugs before they became walled off—in which case we can hopefully accept the calcification as "evidence of healing". At the moment, I believe that while calcification which occurs before drug treatment is started may harbour living tubercle bacilli, and may therefore be dangerous, the calcification which develops during treatment may be sterile and safe. Only time will provide the correct answer.

Postural drainage.—A special problem arises when a patient has a bone or joint lesion combined with a renal lesion.

Immobilization of a patient by any type of apparatus which prevents his turning over in bed has a profound effect upon urinary drainage, even in young people. We have found that secondary urinary infection develops rapidly in these patients and they tend to have a deposit of mucus and phosphate in the base of the bladder.

The daily turning of a patient in a spinal frame is a great problem in these days of nursing shortage but it is a vital necessity in some cases. This problem was brought to our notice by the occurrence of a dirty urine and hæmaturia following the turning of several patients who had been lying on their backs for some weeks undisturbed.

We now try to turn them daily until the dirty urine and bleeding subsides, after which the strain on the staff can be eased.

Urinary obstruction and hypertension.—Finally we must refer to an alarming problem which has only just become evident to us (Table III). 36 of our 104 patients have had, or still have, radiological evidence of some obstruction at the pelvi-ureteric junction or at the uretero-vesical junction. 17 of these 36 patients are hypertensive. Of these 17, 13 are under 35 years of age, and they are all under 45.

15 of these 17 patients show unmistakable radiological evidence of obstruction to the outflow of one or both kidneys. The remaining 2 patients have had the obstructed kidney removed but remain hypertensive.

In this small series, 3 patients are in a state of malignant hypertension. They have had bilateral disease for more than five years and have each had a closed pyonephrosis removed.

Reference to Table III shows that 19 of the patients with urinary obstruction are not

TABLE III.—HYPERTENSION RELATED TO URINARY OBSTRUCTION

(Total series 104 patients)

36 patients have (or had) obstruction on one or both sides.
17 of these are hypertensive:
2 of these are still hypertensive after removal of an obstructed kidney.
3 are in a malignant state.

Hypertension = Pressures in excess of 140/95 mm.Hg.

hypertensive. However, to our certain knowledge, the obstructive element has been present for less than a year in half of them, and it could easily be that there has not been time as yet for hypertension to develop. We have watched the blood pressure rise in two cases over a period of six months. One young man developed a closed pyonephrosis, the removal of which restored his blood pressure to normal. The other, a most encouraging result, had his pressure reduced by an ileocystoplasty which markedly relieved a serious ureteric reflux.

Looking at these figures impartially, there are as many patients with obstruction and a normal blood pressure as there are patients who have obstruction and hypertension, but *all* of the hypertensive patients show signs of obstruction. One cannot help suspecting the obstructive or fibrotic element.

In any event, the incidence of hypertension in 17 of our 104 patients is alarmingly high, particularly if we remember that 13 of them were under 35 years of age. One can only hope that this is a coincidence which will not be repeated in a larger series. However, we are to-day undoubtedly preserving kidneys which a few years ago would have been removed on sight, and this problem will have to be studied very carefully.

At the present time we are in favour of nephrectomy for cases with obstruction in the presence of hypertension, but are prepared to wait and watch in the absence of hypertension. We are certainly most ardent supporters of conservatism, but would hesitate to exchange a healed tuberculous kidney for hypertension in a young person.

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There was a valuable discussion in which the following took part: **Dr. W. A. Murray**, Edinburgh; **Mr. Norman Slade**, Bristol; **Mr. J. Cosbie Ross**, Liverpool; **Dr. R. C. B. Pugh**, London; **Mr. J. G. Gow**, Liverpool; **Mr. R. T. Turner Warwick**, London; **Mr. C. I. Murphie**, London.

Clinical Section

President—Sir HENEAGE OGILVIE, K.B.E., D.M., M.Ch., F.R.C.S.

[*March* 8, 1957, contd. from July *Proceedings*, p. 516]

MEETING HELD AT THE WHITTINGTON HOSPITAL, LONDON

Spontaneous Gastro-jejunostomy.—W. W. DAVEY, M.D., F.R.C.S., F.R.C.S.I.

This case is presented because it is the first record of a spontaneous gastro-jejunostomy due to a gastric ulcer.

Past history.—Mrs. E. S., now aged 72, developed gastric symptoms in 1930 when at the menopause. There is little doubt that her symptoms were due to a gastric ulcer for she was admitted to University College Hospital in 1931 and again in 1933 for six weeks on each occasion, and from 1935 till 1939 she was under the care of Lord Horder at St. Bartholomew's Hospital, including six weeks as an in-patient. While in these hospitals she had three barium meals, all of which showed a low lesser-curve gastric ulcer. Only one fractional test meal was done; this showed free and combined acidity within normal limits. In 1941 she was investigated at the Royal Northern Hospital and considered to have rheumatoid arthritis.

Present history.—She first came to the Whittington Hospital in July 1950 and since then she has been an in-patient for long periods on six occasions.

She was first admitted on account of a right femoral vein thrombosis, but while in hospital she was found to have the blood picture of a macrocytic anæmia, possibly pernicious anæmia as suggested by blood counts, sternal marrow examination, repeated histamine-fast achlorhydria and her response to liver and vitamin B_{12}.



FIG. 1.—Barium meal (3.12.52) showing shortening and scarring of lesser curvature in region of angulus.



FIG. 2.—Barium meal (26.1.54) showing hour-glass spasm of the stomach with ulcer on the lesser curvature.



FIG. 3.—Barium meal (1.12.54) showing gastro-jejunal fistula.

Because of her dyspeptic symptoms and her previous gastric history a barium meal was carried out; it showed a low lesser-curve gastric ulcer. Barium meal studies were repeated at fairly frequent intervals because she was known to be achlorhydric; they all revealed deformity in the region of the angulus suggestive of a gastric ulcer, of which Figs. 1 and 2 are examples. Gastroscopy was performed on three occasions and this confirmed the "hour-glass" like deformity of the lower stomach with pouching out of the greater curve and scarring above the angulus on a shortened lesser curve. During many barium meals the radiologist (Dr. W. Stachurko) had commented on several occasions on the rapid passage of barium into the jejunum but not till December 1, 1954, did he venture to suggest that a gastro-jejunal fistula existed (Fig. 3).

RÉSUMÉ OF INVESTIGATIONS

Blood:
27.7.50: Hb 53%, reticulocytes 2%, R.B.C. 2,500,000, P.C.V. 22%. Marked anisocytosis and poikilocytosis. There was a reticulocyte response of 7·5% six days after starting vitamin B_{12}. (The dosage of vitamin B_{12} used was: 4.8.50, 80 mg.; 22.8.50, 80 mg.; 5.9.50, 100 mg. Cytamen every two weeks.) Before vitamin B_{12} was given the reticulocytes averaged between 1% and 2%.
23.11.50: Hb 82%, R.B.C. 3,800,000, P.C.V. 37·5%, on vitamin B_{12} and iron.
9.2.51: Hb 80%, R.B.C. 4,400,000. Film normal.
31.12.52: Hb 66%, R.B.C. 4,200,000, P.C.V. 33%.
25.3.53: Hb 70%, R.B.C. 3,500,000.
12.11.54: Hb 70%. Group B, Rh-positive.

Marrow:
20.9.50: Megaloblastic liver deficiency anæmia.
9.10.50: Normoblastic but hypercellular on vitamin B_{12}.
31.3.53: Hypoblastic iron deficiency and early stages of a deficiency of the liver factor.

Fractional test meals:
28.7.50: Achlorhydria.
8.12.52: Achlorhydria with histamine.
31.12.52: Achlorhydria with histamine.
26.11.54: Achlorhydria, Kay's augmented histamine.

Barium meals:
25.10.50: Suggests low lesser-curve ulcer. Rapid emptying and irregularity of incisura which is suspicious of malignancy.
21.11.50: No change.
9.2.51: Well-defined low lesser-curve ulcer. No malignancy.
2.12.52 and 9.2.53: Scarring of low lesser curve suggesting ulceration.
1.12.54: Chronic gastric ulcer with early hour-glass deformity. Barium seen to pass from stomach into jejunum.

Gastroscopy:
6.1.53: Stomach shows classical "tea-pot" deformity with great shortening and scarring of the lesser curve. No sign of malignancy. Pylorus not seen.
4.5.53: No change.
8.11.54: No change.

Operation (December 1954).—Following the discovery of a gastro-jejunal fistula surgery was considered necessary. Laparotomy revealed a perfectly performed, posterior, retrocolic, short-loop gastro-jejunostomy. There was no tumour, no enlarged lymph glands and no evidence of active ulceration. The lower stomach was deformed showing shortening of the lesser curve and scarring of the anterior wall of the stomach in the region of the angulus. The gastro-jejunostomy was dismantled, the jejunum repaired and a Billroth I gastrectomy performed (Fig. 4 A and B).

Follow-up.—In the two and a half years since operation she has had no gastric symptoms. A barium meal shows a normally functioning Billroth I gastrectomy. Her weight has been maintained at slightly below the pre-operative level. She has received no anti-pernicious-anæmia treatment and her blood picture has remained normal apart from a mild microcytic anæmia which one might expect with chronic rheumatoid arthritis. A test dose of radioactive vitamin B_{12} was normally absorbed and estimations of vitamin B_{12} in the serum were within normal limits. The diagnosis of pernicious anæmia cannot therefore be upheld.

RÉSUMÉ OF INVESTIGATIONS

Blood:
18.8.56: Hb 67%, R.B.C. 5,100,000, P.C.V. 36%. Film normal.
12.12.56: Serum vitamin B_{12} 350 $\mu\mu$g. per ml. (normal 120–900).
February 1957: Test dose of radioactive vitamin B_{12} normally absorbed.
Kay's augmented histamine test (26.2.57): Achlorhydria.
Barium meal (5.9.56): Normal Billroth I gastrectomy.
Gastroscopy (5.9.56): The entire pouch was seen and considered to be normal. Three biopsies were taken from high on the posterior wall using Wood's forceps.
Gastric biopsy (6.9.56): Inflammatory hyperplasia.

Morbid anatomy and histology.—The resected specimen is a sleeve of stomach. The serosa is smooth and shiny and there is a deficiency on the posterior wall (2·5×1·5 cm.) representing the stoma of the spontaneous gastro-jejunostomy (Figs. 5 and 6).

Microscopy (Dr. S. H. G. Robinson).—"Chronic inflammation and fibrosis of the wall of the stomach in the margin of a gastro-jejunal stoma and conspicuous adenomyosis with greatly dilated ducts in the remainder of the wall of the stomach."

No record of such a fistula can be traced in the literature. C. C. Gardner (1955, *Postgrad. med. J.*, **31**, 16) has described one resulting from a gastric neoplasm.

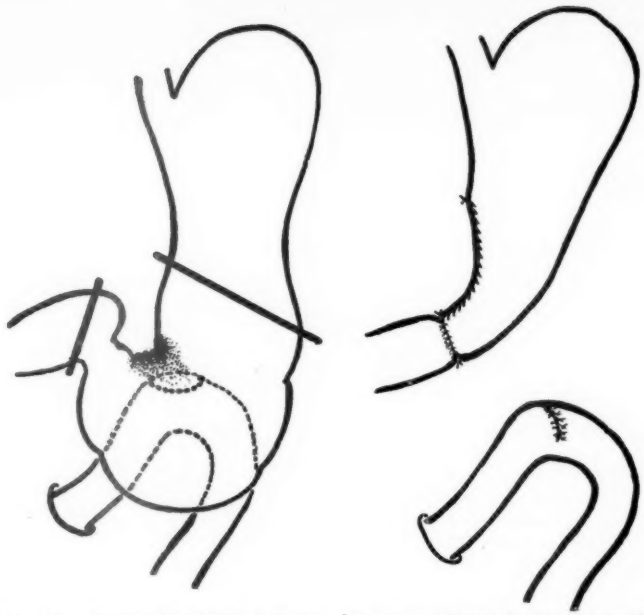


FIG. 4A.—Dismantling of spontaneous gastro-jejunostomy.

FIG. 4B.—Billroth I gastrectomy with repair of jejunum.

(Drawn by Mr. H. Collinson, F.R.C.S.)

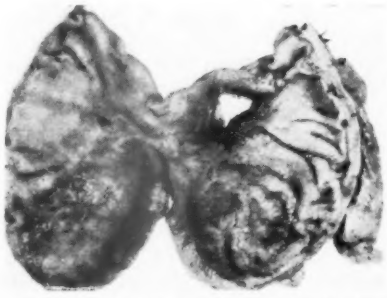


FIG. 5.—Operation specimen opened along the greater curvature showing scarring of the lesser curvature and the gastro-jejunal stoma on the posterior wall of the stomach.



FIG. 6.—Operation specimen viewed from behind showing gastro-jejunal stoma with fringe of jejunum attached to stomach.

Conclusion.—The original lesion was a chronic innocent gastric ulcer. Some time between 1950 and 1954 or perhaps earlier a spontaneous gastro-jejunostomy developed because the ulcer became adherent to and finally penetrated a high duodeno-jejunal flexure. A gastro-jejunostomy alone does not account for macrocytic anæmia, there must be some additional factor—in this case severe gastritis with adenomyosis of the stomach. Gastric surgeons are often blamed for causing anæmia by their operations; it is a pleasure therefore in this case to have cured one.

Acknowledgments.—I wish to thank Dr. A. L. Jacobs and Dr. K. C. Robinson, under whose medical care this patient has been.

Hepato-lenticular Degeneration.—MICHAEL ASHBY, B.M., M.R.C.P.

Girl, aged 13 years.

Her condition rapidly deteriorated to the point of grave incapacity. Treatment appeared to arrest the deterioration completely and to bring about a material improvement in mobility but much less so in speech.

History.—1953: The condition presented at the age of 13 with slowness of speech and movement and marked deterioration of school performance.

August 1953: Signs of Parkinsonism were found and she was started on stramonium. The condition slowly progressed.

February 1954: Right spontaneous pneumothorax. Admitted to hospital. No Kayser-Fleischer rings or hepatomegaly were noted. On discharge she was put on Artane, but took this somewhat erratically.

June 1954: Admitted for dental treatment.

September 1955: Gait now very slow and severe dysarthria. Examination showed Kayser-Fleischer rings, and she was readmitted to hospital.

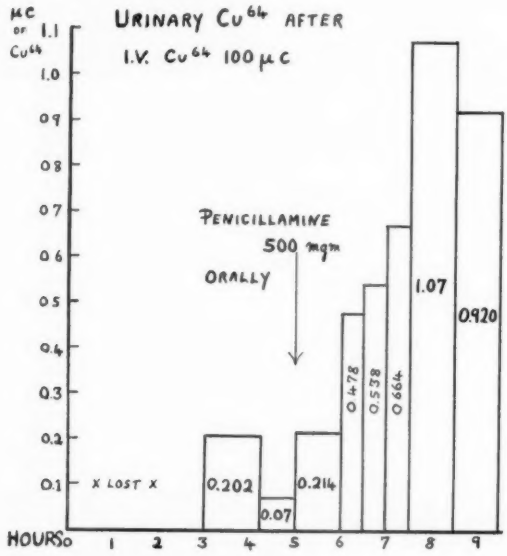


FIG. 1.—Chart of radioactive copper excretion showing greatly increased output in the urine following administration of oral penicillamine 500 mg.

Copper metabolism was investigated by Dr. J. N. Cumings of the National Hospital, Queen Square, and she was subsequently treated with B.A.L. and potassium sulphide.

	Serum copper	Oxidase activity
Normal	70–150 μg./100 ml.	120–180 μl. of oxygen/ml. per hour
Patient, before B.A.L.	59	Nil
after B.A.L.	43	11·6
Parents and 4 sisters ..	110–143	123–148

Considerable improvement in mobility and reduction in spasticity were noted after the three courses of B.A.L.

The patient was then transferred to the Medical Unit of University College Hospital where Dr. J. M. Walshe undertook further studies, including radioactive copper excretion (Fig. 1).

Greatly improved copper excretion was obtained after oral penicillamine, 500 mg.

A marked further improvement was obtained in the patient's mobility, and she again became able to hurry and even to run. Speech, however, has improved very little and dysarthria is still very severe.

Section of Anæsthetics

President—KATHARINE G. LLOYD-WILLIAMS, C.B.E., M.D., F.F.A.R.C.S.

[*February* 1, 1957]

Resuscitation of the Burned Child

By D. W. SHANNON, M.B., Ch.B., F.F.A.R.C.S., D.A.

Consultant Anæsthetist,
Royal Hospital for Sick Children, Edinburgh

BURNS are to-day a serious social problem ranking second only to motor vehicle accidents as a cause of death, or injury in children. Any minute, any hospital in the country may admit a seriously burnt child. As a member of the Surgical Team, the Anæsthetist must be prepared, therefore, to assist, or, if necessary, assume responsibility for the immediate care of a child in a state of oligæmic, or "burn", shock.

CLINICAL ASSESSMENT

When treating the burned child, a clinician has two problems on his hands, (1) the child, and (2) the burn. He must firstly protect the child from those inherent weaknesses, which, under the circumstances, may endanger his life, and secondly, from the pathology associated with the burn.

There is one point relevant to this discussion which I should like to emphasize, i.e. the child's tremendous thirst for oxygen, a 5-year-old child (the average child) requiring 5–6 c.c./kg. body-weight/minute compared with 3·9 c.c. in adults. Even at rest, the child's heart and lungs are working half as hard again as those of the adult. He has not, therefore, the tremendous respiratory and cardiovascular reserves that the adult has to fall back upon in times of stress.

This is the reason why a child's condition deteriorates rapidly following a serious injury. It is the reason why the assessment of such a case is based upon the functional efficiency of the respiratory and cardiovascular systems. Because of the rapidity with which the vital reserves are depleted, this assessment should be determined from clinical observations: the colour of the child, the feel of his pulse, the capillary filling time, the child's temperature, the dryness, or dampness of his skin, the rate and depth of his breathing, and his muscle tone. Such observations give an immediate and reliable indication of the efficiency of the child's vital systems. Special investigations and laboratory findings are delayed and may be misleading. It is against this background that the patho-physiology of a burn must be considered.

Cope (1951) has compared the burn wound to a leech, which sucks water, protein and electrolyte from the plasma circulating in its depths. The volume of fluid lost is proportional to the extent of body surface burned, and the leakage continues for forty-eight hours, the loss being greatest during the first eight of these hours. The result of this fluid loss is to lower the circulating plasma volume, interfere with the hæmodynamics of circulation and so reduce its efficiency. In deep burns, this efficiency may be still further impaired by red blood cell destruction.

The child's response will depend upon the volume of fluid lost. Following extensive burns, which, for my present purpose, I shall take as burns involving more than 10% body surface, the child is unable to accommodate the loss. The clinical picture during the hours immediately following injury is one of thirst, pallor, and restlessness. These signs indicate a mobilization of his fluid reserves and are a silent demand for fluid. If this demand is ignored, the child's fluid reserves will be drained and his cardiovascular system will no longer be able to carry out its normal physiological function. The child's condition will

deteriorate rapidly, his blood pressure will fall, his pulse-rate will rise, and he will become cyanosed, apathetic and later comatose. In such cases, fluid replacement is a matter of the utmost urgency and must be given intravenously.

The healthy child, with less extensive burns, has reserves which are capable of sustaining him during the early hours when fluid loss is greatest. Fluid replacement is, therefore, less urgent and his requirements may be given by mouth. These cases, however, are potentially dangerous because not all children are healthy. Many have a chronic illness (bronchitis, anæmia, malnutrition), which has already sapped their reserves. In such cases, the fluid loss occurring in a 6–10% surface burn may be sufficient to drain those reserves and precipitate oligæmic shock. Vomiting is the earliest sign of trouble in these borderline cases and an immediate indication to discontinue fluids by mouth and substitute intravenous replacement.

Intravenous Fluid Replacement Therapy

The literature has emphasized the danger of over-infusing children. This propaganda has encouraged clinicians to err on the safe side and give too little rather than too much. Yet the effect of under-infusing an extensively burnt child will be even more serious.

To effect a happy compromise between too much and too little, the nature and volume of the fluid and the rate at which it is given must be carefully assessed. Ideally, it should be similar to the nature, volume and rate of fluid loss. The assessment is based upon certain specific information:

(1) The time which has elapsed since injury and the treatment that has already been given.

(2) The weight of the child.

(3) The depth and extent of the burn, the extent being estimated from a simple diagram based on Berkow's tables (Fig. 1).

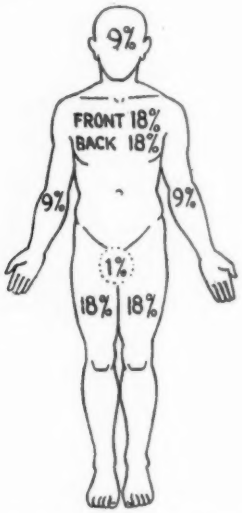


Fig. 1.—"Rule of Nine" for estimating area of burn.

The *nature* of the replacement fluid depends upon the depth of the burn. A superficial burn is given reconstituted plasma, a fluid which is similar to the burns exudate. A deep burn, however, must be given whole blood in addition to plasma in order to replace the red cells destroyed, or damaged, in the depths and at the periphery of the wound. The hæmoconcentration, which occurs in the hours immediately following a burn, is not a contra-indication to the giving of blood. Indeed, its administration at this time is necessary to delay and to limit the characteristic anæmia, which will later complicate the stage of healing.

Many formulæ have been devised to assist the clinician in assessing the *volume* of fluid required to replace that lost into the burn wound during the forty-eight hours immediately following injury. In Edinburgh, the formula used is based upon the extent of the burn

and the child's weight, 3 c.c. colloid fluid being given/1% surface area burned/kg. body-weight (e.g. a child weighing 20 kg. with a 20% burn would require 1,200 c.c. fluid).

The *rate* at which it is given is indicated by the extent of the burn and the time that has elapsed since injury. Following a burn of less than 30%, one-third of the estimated total replacement volume is given in the first four to six hours following injury, this period being calculated from the time of injury and not from the time of admission to hospital. A second one-third is given during the next twelve to sixteen hours, and the final one-third during the remainder of the forty-eight-hour period. These figures are a guide to therapy. The object in treatment is to get the child out of shock as quickly as possible to protect him from the harmful effects of prolonged tissue anoxia. The rate, therefore, will ultimately depend upon the clinical response of the child.

Following more extensive burns, or when intravenous therapy has been delayed, it may be necessary to give as much as two-thirds of the total replacement volume in the first few hours following injury to prevent early death due to shock, or, if this be averted, hepatic and renal failure due to prolonged anoxia. The total volume given, however, remains the same; only the rate is altered.

Following a deep burn, a part of the estimated replacement volume has to be given as whole blood. The volume given depends upon the red blood cell loss, which may amount to 20–40% of the red blood cell volume, depending upon the extent of the burn, e.g. a child with a blood volume of 1,600 c.c. and, therefore, a red blood cell volume of 720 c.c. would, following a 30% deep burn, have to be given 140 c.c. of red blood cells, i.e. 300 c.c. of whole blood as part of the estimated total fluid replacement volume.

Assessment of Progress

The efficiency of treatment is assessed by:

(1) The clinical response of the child, his colour, warmth of skin, lessening of thirst and diminishing restlessness.

(2) The hourly urine output. This is obtained by means of an indwelling catheter and is the most important single guide to the patient's response.

Throughout the period of oligæmic shock, the urine output is reduced through the action of anti-diuretic hormone (A.D.H.), which is released as a part of the child's response to injury. A reasonable output, therefore, for a 1-year-old would be 8–10 c.c., for a 5-year-old 12–15 c.c., and for a 10-year-old 18–20 c.c. It is the changes in the hourly output that are important, however, rather than the absolute volume. A steady output in the region of those figures I have mentioned or a rising output, which becomes stabilized after a few hours, indicates a satisfactory response; whereas an output which continues to increase from hour to hour or which, after increasing and stabilizing begins to fall, indicates in the first instance that too much fluid is being given and in the second too little.

Following a deep burn, anuria may occur as a result of the hæmoglobin released by red cell destruction. Normal healthy kidneys are capable of dealing with large quantities of hæmoglobin. The kidneys of a severely burned child, however, are not functioning normally. Renal anoxia, an associate of oligæmic shock, together with the increased reabsorption of fluid following the release of A.D.H. concentrates hæmoglobin in the distal tubules and may precipitate lower nephron nephrosis, and a renal shut down. This danger may be anticipated by identifying hæmoglobin in a scanty urine, and averted by:

(1) The prompt and effective treatment of oligæmic shock.

(2) The intravenous infusion of mannitol.

This high molecular substance reverses the effects of A.D.H. and by retaining water lowers the concentration of urinary solutes, including hæmoglobin, in the tubules.

Metabolic Fluid Requirement

Fluid replacement therapy takes no account of the metabolic fluid requirements—of the daily loss of water through the lungs, kidneys, skin and bowel. Water must, therefore, be given in addition to blood and plasma. It must be noted that because of the oliguria and skin destruction associated with a burn there is a reduction in water loss. The water intake during the first few days must, therefore, be reduced correspondingly and indeed in certain cases it may be necessary to reduce the normal metabolic fluid requirements by half. These requirements are satisfied by small hourly drinks, which should be given after the child has been brought out of shock and the danger of vomiting has passed. Serum sodium estimations indicate the accuracy of the assessment. Normal serum sodium is 140 mEq./litre. This level should be maintained. A fall indicates that too much water is being given and forewarns water intoxication.

Following burns of less than 10%, fluid replacement is less urgent and the child's requirements may be satisfied by drinks of half-normal crystalloid, 6 c.c. of sweetened half-normal saline/kg. body-weight/1% burn being given in small hourly fractions. The metabolic fluid requirement must be added to this volume, less restriction of water being necessary in these cases because the effect of A.D.H. is less marked.

Supportive Measures

Though fluid loss is the cause of oligæmic shock and fluid replacement, therefore, urgent and imperative, it must be remembered that the effect of shock is anoxia and it is tissue anoxia, which changes it from a reversible process into an irreversible state. Besides restoring the circulating blood volume, every effort should be made to ensure that the other systems concerned with tissue oxidation are functioning adequately.

Serious respiratory embarrassment is readily recognized and commands immediate attention. Minor incidents may, however, pass unnoticed, yet, if allowed to persist, they will exaggerate the anoxia of oligæmia and possibly endanger the child's life.

The oxygen supply may be interfered with in a variety of ways:

(1) The respiratory centre may be depressed by the indiscreet use of sedatives, or stimulated by anxiety or fear to produce a rapid, shallow breathing, which is exhausting and inefficient.

(2) The respiratory muscles may be damaged, or their action interfered with following burns of the chest and abdomen.

(3) The respiratory passages may be obstructed by: (*a*) laryngeal and pulmonary œdema following the inhalation of noxious gases. (*b*) Pressure upon the trachea due to œdematous fluid accumulating deep to the inelastic eschar of a circumferential burn of the neck. (*c*) Crusting of secretions within the vestibules of the nose. This is a common occurrence following burns of the face. It results in mouth breathing with all its harmful effects and in the accumulation of thick viscid post-nasal secretions, which ooze down into the laryngeal region causing exhausting bouts of coughing, and respiratory embarrassment.

The child's weakness is his thirst for oxygen. As long as his supply and its transport is restricted, therefore, every effort must be made to cut down as far as possible his tissue demands for oxygen.

Handling should be reduced to a minimum, only essential diagnostic and therapeutic measures being permitted.

Restlessness must be controlled by adequate fluid therapy and the control of pain and anxiety by the careful use of opiates.

Acknowledgment.—I wish to thank Mr. A. D. R. Batchelor and Mr. A. B. Wallace for their encouragement and help in the preparation of this paper.

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Anæsthesia for Burned Children

By Harry Middleton, F.F.A. R.C.S.

Consultant Anæsthetist, Welsh Regional Burns Unit, St. Lawrence Hospital, Chepstow

The present tendency to admit burns chiefly to special centres has resulted in burned children becoming the province of a relatively small number of anæsthetists. This paper is based on experiences with 500 burned children admitted consecutively to the Welsh Regional Burns Unit, Chepstow, of whom 21 died. 199 of these children required no surgery, but the remaining 301 underwent 502 procedures under general anæsthesia. 10% suffered from infectious diseases on or after admission, and many had other complications such as are found in overcrowded and poor living conditions which themselves increase the risk of being burned (Tempest, 1956).

Adequate resuscitation is essential; for this, the chart of Lund and Browder (1944) simplifies the assessment of the burn, and a guide to the chances of death in each case may be obtained from the probit analysis of Bull and Fisher (1954).

Personal contact with these children is the first essential for success. They arrive in hospital having suffered the most terrifying experience of their lives, they may be gravely ill, and they are going to be submitted to the ordeal of resuscitation and in many cases to multiple operations. Everyone in the unit must be a friend—the anæsthetist among them.

It is therefore preferable that the latter's visits should be frequent and made in his theatre clothing. The anæsthetist is going to be glad of all the co-operation he can get, and familiarity may obviate the need for heavy sedation which he will be unwise to use.

Breathing exercises are instituted by the physiotherapists from the day of admission, and the use of a detergent aerosol to loosen mucus has been found of value. Some chest complications, however, are very intractable though they must not be allowed to delay operation once the time is ripe for surgery. A very few are undoubtedly due to the inhalation of smoke and hot gases and these patients must be checked for carbon monoxide poisoning, but Wakeley in 1941 and Wyatt and Khoo in 1950 described the presence of fat embolus in fatal burns and it is very probable that some of the cases which we describe as "chesty" pre- or post-operatively are suffering from this condition. This problem is undergoing investigation at the moment. It is possible that if fat embolus is implicated, one of the intravenous emulsifying agents may be found to be of use. The anæsthetist, then, is faced with complications which in most other branches of surgery would cause him to advise postponement, but this should be avoided in the treatment of a burn. Even though the patient's condition may appear critical, any delay will lead to deterioration and the anæsthetist's acceptance of the risk may be life-saving.

As it is seldom practicable to weigh a severely burned child, the pre-anæsthetic sedatives must be chosen on a basis of assumed weight, with due allowance for toxæmia, pyrexia and depressed renal function. (The urinary chlorides should be estimated frequently by the Fantus test (Prendiville, 1954).)

I prefer to give papaveretum by intramuscular injection about an hour before operation, in the dosage recommended by Anderson (1951); the infants have pentobarbitone sodium by mouth up to 0·7 grain per stone (7 mg. per kg.).

Atropine complicates the regulation of temperature and therefore the dose should be minimal.

The severely burned child is largely deprived of her most important heat-regulating organ—the skin, by loss as burn and by loss as donor site. She is first of all rendered hypothermic by exposure under anæsthesia and by cold transfusions and then rendered potentially hyperpyrexial by bulky dressings which prevent normal heat loss. In hot weather, especially when humidity is high, these children must be supervised most carefully. An indwelling rectal thermometer with a remote dial will be found useful.

The premedication ordered at the initial pre-operative examination may be the first of many and moreover it will err, if at all, on the safe side. In the course of the last six years I have developed a cumulative anæsthetic record system. This has proved of great value, not only in burns, but also in all the other multiple anæsthetics of pædiatric and plastic surgery.

The object of this system is to ensure that experience of an individual response to premedication, anæsthesia and recovery is carried forward for the benefit of future procedures after making allowance for discrepancies due to mistiming of the premedication or to altered age or circumstances.

The choice of the anæsthetic to be used in the surgery of the severe burn should be governed principally by experience in the use of an agent rather than by the agent itself. Edwards and his associates (1956) in their report on a thousand anæsthetic deaths note the serious implications of departure from accepted practice and I would suggest that the severely burned child is not a subject for the use of unfamiliar drugs or techniques.

In this series we have used a variety of drugs and methods, but the majority of infants, and the more severely burned of the older children, have been induced with cyclopropane and oxygen and maintained with methyl n-propyl ether, oxygen and nitrous oxide. Most of the remaining children have had thiopentone, gallamine and nitrous oxide.

I have followed Hewer's (1955) plan and have had the anæsthetic room ceiling decorated with an attractive washable wallpaper with coloured tropical fish. This provides excellent diversion for the child who is not asleep.

Cyclopropane has a vapour density of 21 compared with 14·3 for air. It may therefore be "poured" over the child's face from a tube concealed within the hand and the child will have no suspicion that it is being anæsthetized (Middleton and Picken, 1954).

A mask is substituted as soon as consciousness is lost and oxygen is added to the cyclopropane.

Anæsthesia deepens very rapidly and usually in a very few breaths the jaw will relax and intubation is performed immediately. I cannot recommend that those who are not

accustomed to the intubation of children should practise this technique of intubation under cyclopropane, as the relaxation wears off in a few seconds and leaves no time to spare. I advocate intubation most strongly and of the 502 anæsthetics given to these children 497 have been by the endotracheal route. Admittedly complications can occur, but they are far outweighed by the advantage of absolute control. With Prendiville I reported 4 cases (Prendiville and Middleton, 1954), none of them fatal, of a condition similar to acute laryngo-tracheo-bronchitis occurring in burned children and Rook (1953) reported three similar. There were no other serious sequelæ and only an occasional transient stridor.

Some burns around the neck and shoulders produce a surprising degree of œdema of the glottis which may embarrass the airway and on occasion we have had to intubate these children for the performance of elective tracheotomy.

Methyl n-propyl ether with oxygen and with nitrous oxide to make up an adequate flow rate is introduced as soon as intubation has been performed and is my choice for the maintenance of anæsthesia, in all infants, and in children who are severely burned. I use a home-made version of the Cardiff connector described by Picken (1950) for the infants, and a Magill or Westminster assembly for the others.

Anæsthesia is kept very light indeed and methyl n-propyl ether has the advantage of flexibility, enabling anæsthesia to be deepened very quickly if need be. Rapid recovery is the rule, and is particularly desirable because a child requires between 60 and 100 ml. of fluid by mouth every waking hour. Pre-operative starvation, and the recovery period, must be cut to a minimum to avoid dehydration.

It is essential that the transfusion be set up as soon as the anæsthesia has been settled and surgery must not start until the drip is going well. Under anæsthesia, veins will appear which were invisible before and it should be a matter of anæsthetic morality not to take an easy vein if a difficult one will do. The external jugular vein is easily needled with a Guest cannula by turning the head to one side and by stretching the vein between the back of the forefinger and the thumb. A breath of strong diethyl ether at the critical moment will cause straining which will dilate the vein and facilitate the procedure. Once the cannula is in, it is sutured in position.

The rate of transfusion should always be kept level with the blood loss, which can be estimated with reasonable accuracy by the use of standard swabs. After use these are counterbalanced by clean swabs from the same batch and the weight in grams used to balance gives the blood loss directly in millilitres.

When replacing lost blood, it must be remembered that a standard bottle of 540 ml. of blood contains 120 ml. of anticoagulant and that deterioration takes place at the rate of 1% per day for the first ten days and more rapidly thereafter. A bottle of blood near expiry therefore has a value of only about 300 ml. and the amount of useless fluid in a late dated bottle must be taken into consideration to avoid overloading.

If at any time it appears that blood loss is overtaking replacement and that shock may occur, the operation must be stopped and the child rested by covering up the wound and by lowering the head of the table. The operation must not re-start until the child is again in reasonably good condition.

The curettage of granulating surfaces to produce a good base for the reception of a skin graft is a procedure which seems to produce shock out of all proportion to the area involved. It is important to anticipate this, to rest the child from the operation at the earliest sign of trouble and to have adequate blood available for rapid transfusion if need be.

I have used elective hypotension on a few children having burns excised, using a drip 1 in 1,000 or 1 in 500 trimetaphan (Middleton and Kunz, 1956). This has produced a substantial reduction in hæmorrhage and has shortened the operating time. The children have been notably unshocked. This technique causes a big saving to the blood transfusion service and avoids replacement by citrated blood. The acid citrate dextrose used to store blood is metabolized rapidly by the liver and is unlikely to influence clotting in quantities which do not produce cardiac arrest, but the transfusion of large quantities of stored blood may delay clotting due to a deficiency of platelets (Stefanini, 1954). The citration of blood also causes a deviation to the left of the oxygen dissociation curve which lasts for several hours (Valtis and Kennedy, 1954). Transfusion of such blood may cause an appreciable diminution of the child's oxygen-carrying capacity and may influence us to give a high oxygen percentage during anæsthesia and in the immediate post-operative period.

Perhaps the worst part of the operation in any surgical treatment of burns is the application of dressings. The burned patient, even without anæsthesia, is singularly susceptible to blood pressure response to changes in posture and even the most careful application of

dressings may cause collapse after an uneventful operation. Treatment is the adoption of the head-low position and if necessary an infusion of l-noradrenaline.

I find that, in practice, the severely burned are best transferred to bed in the theatre before withdrawal of the anæsthetic. I then set up an oxygen tent but continue to administer oxygen through the anæsthetic circuit until the tent oxygen concentration is high enough.

An oxygen tent, newly erected, increases its oxygen content at a rate of roughly 1% per minute at a five litre per minute flow, so it is important not to be lulled into a false sense of security by its presence. A concentration of 50% should be obtained before the supply delivered directly to the child is disconnected.

In order to hasten the increase, a secondary oxygen supply is introduced into the tent (Middleton, 1955), as it is not possible to introduce a high flow through the normal inlet, in most tents in use in this country.

All our patients undergoing surgery return to recovery wards in which oxygen and suction are piped to each bed. We have had six and a half years' experience of these wards and we are convinced that they are essential for really efficient management of post-operative patients.

21 deaths occurred in this consecutive series of 500 children. Many of these had no hope of survival and others did not undergo surgery before they died. Of concern to the anæsthetist are the 6 who died following surgery:

I. *Christine*, aged 7, arrived moribund with a 60% full-thickness burn. She was resuscitated, but by the ninth day she was so toxic that it was decided to excise dead tissue. 39% of the body surface was removed in stages over two hours and twenty-five minutes using 150 mg. of thiopentone with nitrous oxide, oxygen, gallamine and pethidine. She was awake and talking at the end of the operation, but she died forty-five hours later from toxæmia and septicæmia.

II. *Carol*, aged 4/12, sustained full-thickness burns of most of her face. She developed enteritis, but was successfully anæsthetized on two occasions for tarsorrhaphy and grafting. She died on the twenty-third day, five days after her last operation as a result of enteritis.

III. *Yvonne*, aged 6, had 70% full-thickness burns. On the fifteenth day the burns on the anterior half of her body were excised. Induction was by cyclopropane and maintenance by methyl n-propyl ether, oxygen and nitrous oxide. Two days later she developed ileus and died on the third post-operative day.

IV. *Christine*, aged 5, had 55% burns, 48% full-thickness. She was in very poor condition, but her sloughs were stripped on the nineteenth day under a similar anæsthetic to the last case. She remained toxic and died forty-eight hours later.

V. *Sheila*, aged 8, had a 54% burn, most of it of full-thickness and circumferential of the chest. She survived four operations with the same anæsthetic sequence, cyclopropane, methyl n-propyl ether, oxygen and nitrous oxide within the first sixty-one days, but on the seventy-first day she succumbed to a sudden respiratory infection.

VI. *Iris*, aged 6, had 45% burns, almost all of them of full-thickness. She had a stripping of sloughs and application of electric dermatome grafts on the twentieth day, anæsthesia being as in Case V. She was in good condition post-operatively, but died with multiple pulmonary infarcts three days later.

These 6 deaths, occurring as they did after 502 operations in 301 children, do not give the impression that surgery or anæsthesia in itself causes any increase in the mortality of burns in children—probably the reverse; and in none of these patients could death be attributed to anæsthesia. The implication is, in fact, that the anæsthetist undertaking the care of a burned child is faced with a patient whose life may be in jeopardy, but by failing to undertake a hazardous anæsthetic he may turn a likely mortality into a certainty.

The essentials of anæsthesia for burned children may be summarized as follows:

1) The personal approach.
2) The acceptance of the very bad risk.
3) The careful choice of premedication.
4) The use of a thoroughly familiar anæsthetic sequence.
5) The complete control of resuscitation during operation.
6) The prolongation of anæsthetic care into the recovery period.

My thanks are due to Mr. Emlyn Lewis and to Mr. Leonard Schofield under whose care these children had been admitted, and to the several anæsthetists, notably Dr. John Greatrex and Dr. Jean Horton who have given those anæsthetics in this series which I have not given myself.

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Mr. Emlyn Lewis regarded the anæsthetist as the physiologist of the Burns Surgical Team, and stressed the importance of close liaison between the surgeon and the anæsthetist in the treatment of the burned patient.

He stressed the magnitude of the problem in view of the massive excisions of full-thickness burns; the importance of blood replacement during such excisions and, also, the value of hypotensive drugs during such excisions.

He also expressed the opinion that, within the not too distant future, surgeons would be carrying out excision of massive full-thickness burns within the first few hours of infliction.

He emphasized that it was not the custom at Chepstow to give repeated anæsthetics for dressing purposes and, in fact, he strongly deprecated such procedures.

Dr. Patrick Shackleton was interested in Mr. Emlyn Lewis' suggestion that it might be of advantage to tackle these children within the first hours after they had been burned. He had worked for some years in a burns unit and had the feeling that there was a brief period within the first few hours of the accident when it might be possible to do surgical excision or other procedures before the onset of hæmo-concentration and shock. He asked whether there was a safe, if short, interval where surgical intervention would be practicable.

Mr. Douglas Jackson: Since the concept of early excision of extensive burns has been raised, I think it is worth mentioning our experience with it.

For the last ten years at the Birmingham Burns Unit it has been our practice to excise and graft small deep burns, such as those produced by molten metal, on the day of injury (Ross, 1950; London, 1953). Since 1954, however, we have extended this to a trial of early excision and grafting in burns large enough to require intravenous colloid resuscitation. The largest area excised and grafted in this way has been 25% of the body surface, and this has been done in patients with burns up to 55% total area, excluding erythema. About 25 cases have now been treated in this way.

The operation is planned to close the wound or at least make it smaller at the earliest moment, and if possible before it has become contaminated, with the aim of lowering mortality, shortening healing time and lessening infection and discomfort.

The operation is a big one, but not technically difficult. It has been carried out in selected cases about six to eight hours after injury as it has usually taken us this time to resuscitate the patient and be sure that the blood volume is restored. An amount of blood is lost which is possibly a little greater than that following delayed grafting at two to three weeks if granulations are removed: it may amount to 1–1½ blood volumes of blood in a child. Swab weighing and controlled blood replacement are required during operation, and pre- and post-operative red cell volume estimations are necessary with burns of more than 20–30% total area to make the procedure safe. These investigations have been done by Dr. E. Topley using radioactive phosphorus or chromium techniques. With burns of more than 40% total area, post-operative blood volume estimations are particularly necessary since an amount up to 50% of the patient's red cells may be destroyed in the body during the first forty-eight hours after burning without visible evidence and in addition to the operation loss measured by swab weighing.

It is early days still to assess results but the procedure is certainly possible, and it appears to be safe *provided that* swab weighing and red cell volume estimations are used. It should be emphasized that this is not an operation upon a shocked patient but on a resuscitated one with a normal blood volume, during what is usually regarded as the "shock period" of the first forty-eight hours after burning.

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BOOK REVIEWS

Text-Book of Orthopædic Medicine. Vol. 1. Diagnosis of Soft Tissue Lesions. By James Cyriax, M.D.Cantab., M.R.C.P.Lond. 3rd edit. (Pp. xiv + 711; illustrated. 45s.) London: Cassell & Co. Ltd. 1957.

It is Dr. Cyriax's thesis that orthodox methods of diagnosis in painful conditions of the locomotor system are slovenly and unsatisfactory. As a corollary of this, many of the treatments which are commonly prescribed are illogical or harmful. It is his laudable objective to remedy this state of affairs by teaching clinical methods of examination which are simple, logical and accurate and which require very few adventitious aids—such as X-rays—to be effective.

Although there appear to be extremely few changes in this edition as compared to the last, the fact that this book has required three editions within ten years suggests that the need for new thought on these problems is widely accepted, and in critically evaluating Dr. Cyriax's provocative contributions one must be quite clear whether one is applying empirical or strictly scientific criteria.

As judged empirically there is much to be said for the use of "shock tactics" and dogmatic statements as a method of impressing points upon the reader, especially if the teaching is aimed at postgraduate students who already have a basic knowledge of the subjects under discussion. It is less certain if it is a legitimate approach in training undergraduates.

For example it is a refreshing challenge to one's accepted beliefs to be told on page 81 that osteo-arthritis of the knee-joint is a symptomless condition except in very advanced cases, and that when symptoms do occur they are caused by the impaction of cartilaginous loose bodies within the joint. However, one must challenge the statement on the same page that osteo-arthritis is a purely degenerative process, since it is well recognized that an inflammatory infiltration of the synovial membrane is usually found if osteo-arthritic joints are biopsied in the acute or subacute stages. On page 365 one is arrested by the bald statement that the conception of a "postural backache" is a figment of the clinician's imagination and again on page 488 that the treatment of backache by postural exercises is actually harmful to the patient.

For each part of the skeleton a comprehensive and systematic method of clinical examination is described, and although it is difficult to accept all the interpretations which the author suggests (for example that there are 6 distinguishable varieties of subdeltoid bursitis, p. 248—or three separate types of tennis elbow, p. 278) this is probably the most important message in Dr. Cyriax's teachings. A systematized approach is undoubtedly useful in examining problem cases, it also trains the clinician's powers of observation to examine cases routinely according to a set pattern.

It is not possible to comment on the unorthodox approaches to treatment which are recommended since, except in broad outline, these are relegated to a separate volume. It seems rather a pity to separate two such interwoven themes. It would seem preferable, if two volumes were necessary, to divide them on a topographical basis rather than to leave the reader frustrated by the desire to learn how to cure the patient he has learned to diagnose so accurately! A list of references at the end of each chapter quoting the authority for some of the more startling statements is another improvement which might well be incorporated into future editions.

This book is well presented and thoroughly stimulating. As such it should certainly be studied by those who are interested in this group of common yet ill-understood conditions. As for the validity of Dr. Cyriax's concepts one is forced to reserve judgment until the results of properly controlled clinical trials are available to prove beyond dispute that his methods are a significant improvement over those which he so abhors.

Atlas of the Commoner Skin Diseases. By Henry C. G. Semon, M.A., D.M.Oxon., F.R.C.P.Lond. Colour photography originally directed by the late Arnold Moritz, B.A., M.B., B.C.Cantab. Revised with the collaboration of Harold T. H. Wilson, M.A., M.D.Cantab., M.R.C.P., D.T.M. 5th edit. (Pp. viii + 375; 153 colour plates. 105s.) Bristol: John Wright & Sons Ltd. 1957.

The fact that this atlas has had five editions is a sure sign of its value. It contains 131 plates illustrating the "commoner" skin disorders and 22 plates of "some less common" dermatoses. Accompanying each plate is a fairly brief text usually describing the disease illustrated and its diagnosis and treatment but sometimes giving a brief account of the

patient photographed. The value of the plates is variable; most of them are excellent but some are rather too crimson. They are mostly well chosen, though in one, the diagnosis given, varicose ulcer, seems improbable. It is a pity that dermatologists should use the ridiculous name varicose eczema. Apart from this the text has been brought up to date satisfactorily. The book is very well produced and has a good index. The value of an atlas of clinical dermatology is a matter of opinion but this is a good one. It can be warmly recommended for those who find such a work useful. Considering the cost of good colour photography the price is most reasonable.

Textbook of Physiology and Biochemistry. By George H. Bell, B.Sc., M.D.Glasg., F.R.F.P.S.G., F.R.S.E., J. Norman Davidson, M.D., D.Sc.Edin., F.R.F.P.S.G., F.R.I.C., F.R.S.E., and Harold Scarborough, M.B., Ph.D.Edin., F.R.C.P.E., M.R.C.P. 3rd edit. (Pp. xii + 1068; illustrated. 60s.) Edinburgh and London: E. & S. Livingstone Ltd. 1956.

This textbook has now attained the dignity of a third edition within seven years, an indication of its usefulness. The authors apologize unnecessarily for the slight expansion since the last edition—the amount of information supplied could hardly be shortened further. The medical student who masters its contents will be well armed for his future clinical studies. Despite the tripartite authorship there is a considerable unity of structure, the text is well abreast of present-day physiological and biochemical thinking, the gaps in our knowledge are indicated clearly and adequate references are given to enable the student to get rapidly *au fait* with such detail as he may require and by far the greater number of the references are in English which is fully justified in a textbook of this type. Sufficient of the history of the subject is included for the modern advances to be seen in their proper perspective. There has been no sparing of illustrations, a number of which are in colour. The diagrams are clear and to the point. Many of the figures are from classical papers, a useful feature. The combination of biochemistry and physiology in one volume has much to recommend it from the student's angle and has been very successful although on occasion this has necessitated a certain degree of over-simplification but this is perhaps a criticism in detail. The format is clear—the proof reading has been excellent and the result is a very satisfactory, readable modern introduction to what can still be described as the "Institutes of Medicine" and which will also be useful to the postgraduate needing a rapid survey of the present beliefs and practices in these subjects. It is to be hoped that the authors will not flinch from their voluntary martyrdom and continue to keep it up to date and within controllable limits.

Hypotensive Drugs. Proceedings of a Symposium on Hypotensive Drugs and the Control of Vascular Tone in Hypertension, held in London on April 5 and 6, 1956, at the Wellcome Foundation. Edited by M. Harington, M.B., M.R.C.P. (Pp. x + 222; illustrated. 50s.) London and New York: Pergamon Press. 1956.

This symposium held at the instigation of the Biological Council brought together a very representative group of chemists and biochemists, pharmacologists and clinicians, to discuss certain aspects of a common problem, hypertension.

Starting with a series of papers on the chemistry and biochemistry of drugs lowering the blood pressure, it ranged through to their pharmacology and clinical application and concluded with a discussion on the control of vascular tone in hypertension. Such combined discussions lead to a clearer picture of the real status of the pharmacology and therapy of the disease. The earlier papers indicated the wide range of substances available and showed up the wide diversity of their biochemical modes of action both centrally and peripherally. Structure and activity relations showed up clearly within various series. In the general discussions on the pharmacology of these drugs, considerable attention was devoted to Reserpine, the β-haloalkylamines, the veratrum alkaloids and tolerance to ganglion blocking substance. All the more important types of drug used were discussed including some of the most recent whose clinical status is still under discussion. The amount of pharmacological information now available is surprisingly large but the difficulties of its direct application were clearly demonstrated when the clinical and pathological aspects came under discussion. Until clearer ideas of the pathology or pathologies of the hypertensive state are available the therapeutic attack has to be to a certain extent empirical, but it is yielding results and these results were well dealt with by the subsequent speakers. The symposium, international as it was in character, performed a useful function in that it made those interested better acquainted with the lines of thought underlying the efforts of the various disciplines and gave them a greater appreciation of the difficulties involved and the editor is to be congratulated on the rapidity with which the whole has reached publication to give an up-to-date summary of how matters stand.

Operative Surgery. Editors: Charles Rob, M.C., M.Chir., F.R.C.S., and Rodney Smith, M.S., F.R.C.S. In 8 volumes and index. (Volume 3 Rectum and Anus. Thorax; illustrated. £5 10s. per vol., Index £2.) London: Butterworth & Co. Publishers Ltd. 1957.

We have already given a warm welcome to Volumes 1 and 2 of this work (*Proceedings*, 1957, **50**, 114). The subjects of the present volume form an interesting contrast in that the first part deals with well-standardized operations on the rectum and anus, and the second with the surgery of the thorax, including such recently developed operations as the closure of atrial septal defects. In the section on the surgery of the rectum and anus, it will be a source of pleasure and confidence to readers that the St. Mark's school is so strongly represented in Lloyd-Davies, Goligher, and Lockhart-Mummery. There is little calling for critical comment, but perhaps proctoscopy is too banal a procedure for inclusion in a work of this kind, and we would have been personally happier if exteriorization rather than excision of pilonidal sinus had been described. The excision operation is responsible for much unnecessary morbidity in the form of prolonged and uncertain healing. In the section on fistula-in-ano, we welcome the use of the much more logical term of ischio-rectal fistula instead of ano-rectal fistula. In the treatment of rectal prolapse we wonder whether the editorial policy of getting the contributor to describe fully merely the operation he thinks the best is not an undue simplification of a very difficult problem.

In the section on the thorax, we are glad to see among the contributors the names of such British pioneers as Holmes Sellors and Franklin. We are sorry, however, not to see Sir Russell Brock's name, though in compensation his junior colleagues of the Guy's school are well represented. It is interesting to see how quickly operations have become standardized which only a few years ago were breath-taking advances. The operation of mitral valvotomy so admirably described by Belcher is an outstanding example. A similar criticism to that made above on the treatment of prolapse of the rectum might perhaps also be made about the chapter on the treatment of reflux œsophagitis. We wonder, too, whether the section on methods of obtaining ideal conditions for open heart surgery is not as yet a little too premature for dogmatic description in an operative surgery textbook. These are, however, relatively minor criticisms, and the main impression left by this third volume is that it has fully satisfied the high expectations aroused by the first two volumes.

Lymphatics, Lymph and Lymphoid Tissue. By Joseph Mendel Yoffey, D.Sc., M.D.Manch., F.R.C.S.Eng., and Frederick Colin Courtice, M.A., D.Phil.Oxon., D.Sc.Sydney, F.R.A.C.S.Hon. 2nd edition. (Pp. vii + 510; illustrated. 60s. 0d.) London: Edward Arnold (Publishers) Ltd. 1956.

This very readable book covers a wide field of physiological and experimental medicine, a field which is largely neglected in the average student's education. The examination of many of the beliefs which appear in the average textbook on the functions of the lymphatics and lymph nodes shows that in many cases experimental evidence of their incorrectness has been available for several decades without apparently penetrating very far into the main body of opinion.

Some of the problems discussed in this book are complicated by the variation between species and what is true for the cat is not necessarily true for the human lymph system. The arrangement follows the orderly system of an initial general survey of the anatomy and geography of the lymphatic system. The next chapter is on the formation of lymph and this inevitably entails consideration of the extracellular body fluid and its distribution in the body. The first real step forward in the understanding of the production of lymph followed Starling's paper in 1896 and his original concepts have stood the test of time. One point which is well brought out is the universal presence of protein in the fluid filtered through the capillaries and experiments are quoted showing how the quantity of this protein in the normal dog may vary from 200 mg. to nearly 800 mg. per 100 ml. in varying states of activity. Using the modern electrophoretic techniques, it is shown that this protein corresponds closely to the plasma proteins. When the volume of the extracellular fluid is considered, it becomes obvious that a very large protein pool exists outside the vascular system and, in fact, the amount of protein in the pool is usually greater than the amount in the blood. The return of the protein to the circulation occurs via the various lymph ducts which drain into the vascular system, of which the thoracic duct is best known. Practically the whole of the protein circulating in the vascular system filters through the capillaries and returns through lymph ducts about once every day. The factors affecting the rate of filtration of lymph through the capillaries are discussed, and in particular, oxygen lack.

In the next chapter, the lymphatic systems of the body, alimentary tract, liver, skin, kidney, bones, &c., and the manner of their function in disease is described. The following chapter deals with the rate of flow, the pressure, and the composition of lymph, and useful tables are given of the quantities of the various electrolytes and non-electrolytes found in lymph.

Chapter V discusses the biological significance of lymphoid tissue and its efficiency and it opens with an important section on the effect of irradiation on the lymph tissues of the body. Interesting experiments on the relationship between the amount of lymphoid tissue and bacterial infection are given and it is shown that an animal brought up in a completely aseptic way had only approximately a quarter of the amount of lymphoid tissue present, however such animals were, without exception, malnourished and usually died. The exact position of the lymphoid tissue in the defence mechanism is discussed at some length and considerable doubt is thrown on many theories. In particular, it has been shown that the "barrier" theory is only partially true. It is certain that production of lymphocytes is one of the main functions of lymphoid tissue.

The following chapter is a study of the lymphocyte itself, its development and its function and here there is considerable conflict of opinion, particularly as regards the relationship between the small and the large lymphocytes, plasma cells and monocytes, &c. In the final chapter, practical considerations concerning the relationship between the lymphatic system and disease, such as œdema, inflammation and malignancy are considered.

In this book the literature has been well and thoroughly reviewed. It is, however, more than a mere compendium of other people's research work. Both authors have contributed much themselves and they are not afraid to give their own opinions clearly, even if these are in opposition to some accepted ideas. The book is well produced with good illustrations and only a few misprints.

Cancer of the Lung—Pathology, Diagnosis and Treatment. By Milton B. Rosenblatt, M.D., and James R. Lisa, M.D. (Pp. xiii + 330; illustrated. 120s. 0d.) New York: Oxford University Press. London: Cumberlege. 1956.

This monograph, to which ten authors have contributed, is based upon a study of material derived from the wards of the New York City Hospital and from private practice. It has as its central theme the early diagnosis of carcinoma of bronchus at a stage at which surgical treatment can offer reasonable hope of cure. The necessity for earlier diagnosis is illustrated by the fact that in only 5% of the patients was operation undertaken before the growth had spread beyond the lung of origin to the regional lymph nodes, or metastasized more distantly. With this aim in view the chapters concerned with physical examination and modes of presentation of the disease contain considerable detail and are fully illustrated by case reports and X-ray photographs. Onset with neuropathy is an unexpected omission, but this is the only major criticism of this aspect of the subject. Bronchoscopy, cytological examination of the sputum, and the adenoma are all accorded separate chapters.

In other respects, however, the book falls short of the stature of a monograph. Such predisposing factors as smoking and atmospheric pollution are dismissed more cursorily than their current importance warrants. Medical and surgical palliative treatment, together with the "psychotherapy" of the cancer patient, have all been included with radiotherapy and suffer relative neglect. The bibliography bears no precise relationship to the text.

Biological Aspects of the Transmission of Disease. Edited by C. Horton-Smith (Pp. viii + 184. 21s.) Published for the Institute of Biology. Edinburgh and London: Oliver and Boyd. 1957.

In this age of increasing specialization in the many different aspects of biological research it is gratifying to see an attempt made to gather together some of the experts in their particular fields and, to quote the editor of this book, " . . . to break down . . . the specialist barriers that have hitherto hindered the dissemination of knowledge and exchanges of view. . ."

The book is a collection of papers presented at a recent symposium of the Institute of Biology on the transmission of disease. It includes 22 of the major papers read and these cover such widely different fields as mycology, bacteriology, protozoology, helminthology and virology, in respect of human, animal and plant disease.

In spite of the apparent sectional nature of the book there is, nevertheless, an overall continuity which is derived from the accent that has been placed on the modes of transmission of pathogenic organisms in general rather than on the organisms themselves. Thus the great importance of the soil as a reservoir for pathogenic organisms among the bacteria, parasitic Protozoa (e.g. coccidia), helminths (e.g. hookworms), &c., is increasingly apparent with each paper read. At the same time one is reassured by the vast range of biological and non-biological factors which govern the dispersal, survival and transmission of these organisms: the growing need of much work on such factors is continually stressed.

The book is a mine of information and will doubtless stimulate many readers to take advantage of the large list of references to more advanced reading matter. There is an interesting chapter devoted to the questions raised at the termination of the symposium. Unfortunately the rather monumental task of correlating the mass of problems and obser-

vations discussed by the speakers has not been attempted: the reader is presumably left to his own conclusions which, on the first reading, will probably be that he knows very little about a great deal.

Textbook of Medicine. Editors: Sir John Conybeare, K.B.E., M.C., D.M.Oxon., F.R.C.P., and W. N. Mann, M.D.Lond., F.R.C.P. 12th edit. (Pp. xvi+861; illustrated. 42s.) Edinburgh and London: E. & S. Livingstone Ltd. 1957.

This medium-sized textbook, now in its twelfth edition, is remarkably successful, and is excellent value at its very moderate price. The whole has been revised, much has been rewritten, and students and general practitioners will find here succinct and readable descriptions which cover the wide field of medicine. The index is not up to this high standard. Whenever a student hears, on a ward round or in a lecture, an unfamiliar phrase, e.g. promin dressings (page 101), anchovy sauce sputum (page 144), axonotmesis (page 696), he ought to be able, on coming home, to look it up in the index of his textbook and so learn more about it. This index is not only incomplete; it is inaccurate, e.g. Queckenstedt's test is *not* mentioned on page 693, and the sedimentation rate is *not* mentioned on page 271. It is to be hoped that before the next edition the index will be expanded and most carefully correlated with the text. Incidentally, the authors might look again at the alleged hexameter on page 611. Try as he will your reviewer is quite unable to scan it.

Pulmonary Complications of Abdominal Surgery. By Anthony R. Anscombe, M.S.Lond., F.R.C.S.Eng. (Pp. x + 121; illustrated. 20s. 0d.) London: Lloyd-Luke (Medical Books) Ltd. 1957.

In this present small volume the author has recorded the work which gained him the Moynihan Prize of the Association of Surgeons, and the M.S. degree. One of the characteristics of present-day clinical research, in both its main subdivisions of physic and surgery, is the use of the tools of biochemistry and physiology. In the past, the physician has made greater use of these tools than the surgeon, the latter having been perhaps too exclusively preoccupied with the morbid anatomical. But the balance is being rapidly redressed, and in the volume under review a surgeon has attempted to throw light on the chest complications of operations by quantitative physiological investigations of the mechanical effects of operation on lung function.

After a brief historical introduction in which the modern era is rightly noted as beginning with William Pasteur's classical article of 1908 on massive collapse of the lung, the author describes his own investigations. He has used modern spirometric methods, and relied chiefly on determinations of the vital capacity and the maximum expiratory and inspiratory rates. Charts are given of the effects on these measurements of a wide variety of factors such as various types of abdominal incision, peritonitis, pain, drugs, dressings, distension and posture.

The degree to which the findings can be applied to post-operative chest complications depends on the degree to which the investigations can be regarded as an index of pulmonary function, and the author rightly recognizes that they are incomplete and imperfect indices. But some of the discussion is unduly simplified. Thus, he tends to equate hypoxia with hypoventilation when there may be many other factors in its causation. The author deserves credit for his energy and initiative, and the work can be accepted as a useful introduction to the problem, but it might perhaps have been better contracted into an article in a surgical journal rather than expanded into a monograph.

Dextran and Its Use in Colloidal Infusion Solutions. Anders Grönwall, M.D. (Pp. 156; illustrated. 20s.) Stockholm: Almqvist and Wiksell. New York: Academic Press Inc. Oxford: Blackwell Scientific Publications. 1957.

This monograph, by one of the group which introduced dextran into medicine, is a comprehensive study of the principles involved in its use as a plasma volume expander and the research aspects involved in its clinical use and manufacture. The last war re-emphasized the need for a solution capable of replacing blood. On the Allied side this was largely solved by the use of the blood-bank and freeze-dried plasma. On the German side high molecular polymers such as Periston (polyvinylpyrrolidone) were used. This latter to a certain extent suffers the disadvantage of the older Bayliss gum saline by remaining unmetabolized in the body too long. While the Allied method was the more logical and more satisfactory, under disaster conditions such a type of treatment would be very difficult to keep going. Dextran has the advantage of not requiring exacting conditions of storage and it can be stock-piled if necessary. It comes intermediate between the non-metabolized polymers and the blood and serum preparations in being completely metabolized, and further is free from the danger of

carrying any latent virus infection. The first chapter discusses in detail the advantages and disadvantages of the various types of replacement solution so far employed and makes the point that blood *per se* is not always necessary in cases of shock. It gives a rational basis on which the best choice of solution may be determined. The succeeding seven chapters deal with the chemistry of the dextrans undegraded and degraded, the adaption of molecular size towards the desired therapeutic effect, the fate of dextran given intravenously, the serology, the therapeutic effect and clinical studies of the use of dextran solutions. In addition, there is a postscript dealing with the most recent references at the time of going to press, a mute comment on the ever-accelerating rate of research. The main medical uses of dextran in the last decade are more than adequately covered, the whole field is thoroughly dealt with, the settled facts indicated, difficulties are not minimized, the gaps in our knowledge are shown and the reader is given ample evidence on which to base his own opinions.

The Swedish Dextran Team have every reason to be satisfied with the work initiated. The translation is adequate and the print and general format very satisfactory and the price for such a specialized publication is very reasonable.

The Principles of Therapeutics. By J. Harold Burn, M.A., M.D., F.R.S. (Pp. ix+278; illustrated. 27s. 6d.) Oxford: Blackwell Scientific Publications. 1957.

This book consists of the lectures given by Professor Burn to Oxford medical students. Apparently this is their only formal instruction in therapeutics. However, the lectures are a useful bridge from the laboratory to the clinic. The information given is condensed but clear, and will repay careful reading. As befits its title, therapeutic dosages are seldom mentioned. These are best learned when actually dealing with the diseases. The senseless rote of lists of doses that plagued the medical student of earlier generations did not add to the interest of pharmacology or materia medica as it then was called. The author's enthusiasm is infectious and he demonstrates in an interesting fashion the facts which form the basis of present-day drug therapy. Working during the most active and successful period of the development of pharmacology, he has been able to indicate in broad outline the rapid increase in the efficiency of drug therapy, the transition from therapeutic nihilism to an almost calm expectancy that few problems are too difficult given time and application. In a short work of this nature a great deal of selection of items of study is to be expected and a degree of individual preference inevitable. This is perhaps the case in the field of the local hormones which Professor Burn has studied and enriched over many years. Pharmacologically, however, this is justifiable as it is an essential feature of so much of drug activity. The principles of biological standardization are described sufficiently, and the last lecture is on biological variation and clinical trials. The tone of the book is essentially practical—the author's views on the use of hypnotics are very down-to-earth—it is interesting to find the virtues of the open air invoked as an adjuvant to the treatment of insomnia. He also stresses very early in the course the necessity of good clinical understanding to inspire confidence in the patient. Altogether the book will serve as a useful substructure for rational therapeutics and will hold the interest of the student wherever he may be. The general layout of the book is good and the price, for these days, reasonable. An interesting book, not only for undergraduates.

Mathematics and Statistics for Use in Pharmacy, Biology and Chemistry. By L. Saunders and R. Fleming. (Pp. x+257; illustrated. 27s. 6d.) London: The Pharmaceutical Press. 1957.

This monograph has been published by direction of the Council of the Pharmaceutical Society of Great Britain "to meet the need of those who practise and study pharmacy for a book which is comprehensive but which will not require for its study an unduly high proportion of their time". The first half of the volume is devoted to a rapid survey of various aspects of mathematics at a standard that corresponds roughly to the advanced level of the General Certificate of Education. Many of these chapters are short, and although they are clearly expressed, it seems doubtful—in spite of the authors' assurances—whether many readers will derive much benefit from them unless they have had a good grounding in the subject beforehand. The second part is devoted to statistical concepts and to their employment in various aspects of biological and biochemical assay.

The book contains many examples that are largely illustrative of problems that arise in medical and pharmaceutical work, and these, together with the set questions and answers at the end of each chapter, will prove of much help to the serious reader anxious to ground himself thoroughly in the principles discussed. But in general the standard of the text is pitched high, and it may be doubted how useful the book will be to anyone who does not combine the advantages of a good school background in mathematics with a taste for the subject itself.



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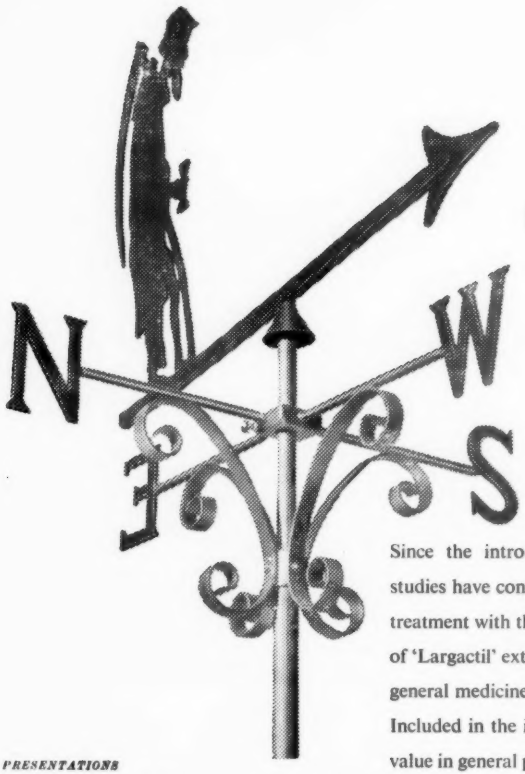
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[*February* 7, 1957]

DISCUSSION ON THE CHANGING VALUES IN ELECTROENCEPHALOGRAPHY

Dr. Denis Hill (Institute of Psychiatry, Maudsley Hospital, London):

The title of this discussion suggests that there have been some significant and radical changes in the theory or practice of electroencephalography. This, I think, has not yet occurred, but I believe we are now in a position to take another look at our subject and to make an attempt at re-appraisal of its techniques and of its usefulness. The history of electroencephalography indicates that in its clinical application it has been necessary always to use an empirical approach. We still have no fundamental knowledge of how the EEG phenomena are produced by neurones, and we have little knowledge of how these phenomena are altered by disease processes. We still do not know with any certainty what physiological functions, if any, these spontaneous electrical rhythms reflect. Interpretation of the EEG record for meaningful clinical purposes has rested therefore upon a basis of approximate correlations. There is little or no physiological logic or meaningfulness in this process, which has been empirical at the lowest level—i.e. a process of correlating EEG patterns with clinical facts without, as a consequence, the development of any theory which can be tested by experiment to account for the associations which have appeared. The lack of a general theory of cerebral functions to take account at once of both the normal and the abnormal EEG is still the greatest defect in the subject. The patterns of electro-cortical activity seen in the experimental animal subjected to lesions in, and stimulation of, different subcortical areas bear striking resemblances in many instances to the abnormal patterns encountered in the human EEG. It has proved very tempting to interpret the phenomena of the abnormal human EEG in terms of the results obtained on the experimental animal. The recognition of the influence which subcortical systems have upon the patterns of the cortical EEG has been the outstanding advance in knowledge of the last ten years.

Nevertheless we must admit that the empirical approach to the subject has failed, since by this method the accuracy of diagnosis—the capacity to answer the clinical problem—has not significantly increased. Rather the reverse has occurred, since with increasing knowledge and experience, the apparent correlations have become less certain. In this respect we can compare the situation of clinical electroencephalography with other empirical techniques in medicine which have proved successful. Generally speaking, most of the measurements of chemical or physiological variables and the single observations of an anatomical or of a structural nature which we can make on man have reasonably hard and fast and therefore predictable associations. It is upon such things that the validity of laboratory techniques rests in clinical medicine. The empirical approach to electroencephalography has failed by comparison. The early work relating simple EEG observations to obvious clinical events has not proved a solid foundation upon which further measurements could be made which, in turn, increased knowledge of cerebral function or led to greater accuracy in topographic diagnosis or understanding of disease process. I would say that, as a result of a single EEG examination and without any clinical information it is rarely possible to predict what is likely to be wrong with a patient. The most useful knowledge the electroencephalographer can possess is clinical information about the patient; indeed, the electroencephalographer must interpret his data in the light of the clinical symptoms. Complete ignorance of the clinical state or an inability to understand the clinical problem which the patient presents, leads to the wildest errors, even in the hands of the most experienced physiologists.

Some of the difficulties which have arisen may have been due to common errors of thinking such as:

(1) First there has been preoccupation with areas of the brain as if they were autonomous units when, in fact, every area is part of a system or systems, disturbance in any part of which may disturb the functions of the area under observation.

(2) As a corollary of this there has been the idea that the disturbance caused by a lesion is necessarily at the site of the lesion.

(3) Thirdly there has been the erroneous idea that there exist electrophysiological or "electropathological" entities having constant clinical associations and a common causation. An example of this is the idea that bilaterally synchronous spike and wave activity is a func-

tional entity with epilepsy as the clinical association and a constitutional or genetic causation.

(4) Then there is the common error of treating the data recorded on the moving paper as if it was a "thing", when in fact what are recorded are only changes of excitability during the period of time under observation. From this another error follows, that there is "an amount of abnormality". We commonly say, for example, that "there is a considerable *amount* of 2–3 c/s activity in the right frontal areas", or there is a "large *amount* of bilaterally synchronous spike and wave activity", suggesting that the greater the "amount" of abnormality, the more pathogenic the lesion, or the more certain it is that a lesion exists, or, by implication, the more serious the prognosis.

In place, therefore, of a spatial anatomical concept of local areas of the cerebral cortex as autonomous units, the electrical functions of which reflect the state of health or disease in them, there is a functional non-spatial and physiological concept of neuronal systems, involving cortico-cortical, intracortical, and subcortical-cortical connexions. Every area of the cortex is involved in all such systems, and the character of the spontaneous electrical activity in any cortical area may be affected by excitability changes in any part of any of the systems in which it is involved, and of which it forms a part. The EEG pattern is therefore sensitive to a large number of different physico-chemical changes but also to structural lesions of all kinds and in many anatomical sites remote from the area under observation. The functional or clinical correlates of changed excitability in these neuronal systems are *not* with motor behaviour or sensory experience, i.e. *not* in altered functions as detected by the methods of classical neurology. Rather it seems that the probable distinctive correlates will prove to be with adaptive psychological functions at a high level, such as learning abilities or conditioning processes. If this proves true we cannot therefore expect to find, and in fact we do not find, hard and fast correlations between EEG phenomena and sensorimotor functions of the C.N.S. In this respect there is a clear contrast with the data of morbid anatomy. Very numerous different clinico-pathological entities may result in the same EEG pattern, and many types of EEG pattern can occur in one disease.

I would like to illustrate this theme by reference to three commonly encountered abnormal phenomena of the EEG. The first of these is concerned with the alpha rhythm and can be described as—*changes of amplitude and occurrence of the alpha rhythm, lateralized to one hemisphere or confined to one area of the head.*

Selective loss of the alpha rhythm on one side of the head is encountered in gross hemiatrophy and is seen, for example, in patients with infantile hemiplegia. In these cases it is assumed that the cortex producing alpha waves is absent. One can, in fact, map out maximal areas of atrophy with some precision by this means and recording the EEG under barbiturate narcosis facilitates the process since the fast rhythm which then develops in normal cortex is absent in atrophic areas. But if many records are taken in such cases it will be seen that the amount of rhythm in the damaged cortex varies from time to time. It is never safe to assume atrophic cortex on the basis of a depressed or absent alpha rhythm in one record. Indeed absent rhythm may mean that a mass of inert tissue, such as a hæmatoma or meningioma, intervenes between the recording electrodes and the brain. But there are often equally important and more commonly encountered cases than this. Reduction or absence of the alpha rhythm may follow a cerebral thrombosis, a contusional blow, a focal epileptic seizure, a surgical procedure and sometimes when there is a space-occupying lesion, either intracerebral or extracerebral, anterior in the head on the same side. In all these cases the actual cortex from which the alpha rhythm is absent is itself normal from the structural point of view. As Williams and Reynell (1945) were the first to point out in the case of traumatic contusion, the site of disease or injury is generally anterior to the areas of depressed alpha rhythm. In these instances we are obviously observing the changed excitability in cortico-cortical systems.

A similar but sudden reduction of alpha rhythm is often witnessed when an epileptic focus starts to fire on the surface of the cortex. This active "suppression" of normal rhythm often precedes the discharge phenomena of the epileptic seizure and no doubt the same cortico-cortical neuronal systems are involved.

The focal abnormality.—The second commonly encountered phenomenon of the EEG is the focus of abnormal activity, and here I shall discuss only the slow wave focus and the focus of spike potentials. *The slow wave focus* is regarded as evidence of abnormal cortical function in the neighbourhood of the electrode from which it is recorded. Walter (1936) was the first to point out the difference between the focus of slow waves having *irregular form* (i.e. varying frequency, amplitude and harmonic content) which is strongly suggestive of local structural disease, and the regular sinusoidal type of slow wave focus not necessarily found in association with organic disease but often found in epileptics. The *organic type* irregular wave form focus is indeed one of the few distinctive, valuable and predictive signs in the EEG, being associated very frequently with structural lesions in the neighbourhood. But again the phenomenon can occur in the absence of such structural disease and

it is most unwise to predict this on the evidence of a single EEG, particularly if the patient suffers from epileptic seizures. A focus of this type of abnormal activity can persist for some days after the seizure in the area from which a focal seizure has started. Serial EEGs spaced over some days are necessary to establish the constancy of the finding. In both types of case, the postictal focus and the tumour focus, depression of the alpha rhythm may be evident as well on the same hemisphere.

In the sinusoidal regular rhythmic slow wave foci, reported first in epileptics, the situation is more complex. These foci occur in normal cortex distant from structural lesions, and for this reason I think the term "physiological foci" is justifiable. They occur in a very large number of disease processes, as well as in epilepsy and in many cases in which there is no known cerebral disease. In the latter these foci are often found in the posterior temporal areas. Yet in other cases where known local lesions of the brain exist, the physiological focus may be also in the posterior temporal areas, when the lesion is elsewhere, perhaps in the other hemisphere. Indeed the physiological focus is always at a distance from the lesion if one is present, e.g. frontal in an occipital lesion, parietal in a frontal lesion, posterior temporal with a lesion in the homologous areas of the opposite hemisphere. Here again one must assume the altered excitability in cortico-cortical neuronal systems. These "physiological foci" are often very sensitive to arousal stimuli, more so than the alpha rhythm, and in this respect contrast with the slow waves in the neighbourhood of lesions.

The spike focus.—The repeated random appearance of spike potentials from one area of the head has not itself any clinical correlations. Brazier (1955) has suggested that these spikes have the same origin as strychnine spikes, namely, that they represent the synchronized discharges of the apical dendrites of large cortical cells, without necessarily any discharge of the cells themselves. The focal spike discharge has been generally accepted as the best evidence we have of a local epileptogenic lesion, be it scar, atrophic gyrus, neoplasm, or vascular anomaly. The spike foci are encountered, it is realized, in the marginal cortex adjacent to the diseased area; the spikes therefore are thought to have localizing value and indeed a wide clinical experience with the EEG gives good support for this view. Electrocorticographic studies have confirmed that the spikes are found in normal cortex around the lesion and moreover that such spikes are often at a considerable physical distance from the lesion. Indeed in many cases of infantile hemiplegia and in some of temporal lobe epilepsy in which focal macroscopic lesions are later found, spike foci have been obtained not only on the atrophic cortex and in the anterior temporal areas near to the lesions, but also *on the opposite hemisphere.* Moreover the firing of the spike discharges on the normal hemisphere is not in any way triggered by those on the diseased side, but is quite independent of them; nor are the spikes on the normal hemisphere necessarily in areas homologous to those on the diseased side from which spikes can be recorded. If one takes a series of EEG records over a few weeks in a cerebral hemiatrophy case or in a temporal lobe epileptic, one is likely to be confused by the fact that the sites of spike foci are not constant, nor is the intensity of their firing constant, from one occasion to another. The ubiquitous but inconstant character of spike foci is baffling to the electroencephalographer who from this data alone is hard put to it to determine which spike focus, out of a possible 4 or 5, is the important one with localizing value. To put the matter in another way, if the patient has epileptic seizures, from which area or areas do the seizures start? Which are the functionally operative area or areas and which are the unimportant ones? There can be no doubt that this is the proper question, for in hemiatrophy cases in which spikes are found on *both* hemispheres, they disappear from the normal hemisphere after hemispherectomy of the atrophic side. The answer to this question at present is, I think, that from spike foci alone the electroencephalographer cannot make a decision; he needs other data. This data may be available in the EEG record—for example, a constantly reduced alpha rhythm in an atrophic area seen over a period of days or in repeated examinations; or may be clinical—the constant aura or focal character of the seizure pattern; or may come from radiology, or from the physical signs. But considered in isolation the single EEG examination may be frankly misleading. In fact, in those cases in which the presenting symptoms are epileptic seizures having a focal character, what elucidation can the single EEG provide? It may show that epileptic spike discharges can certainly be recorded from the expected area. This is satisfactory because on clinical grounds it was suspected, but if one is already confident on clinical grounds that focal epilepsy is occurring, it is merely irritating and solves nothing if the EEG is normal. However, an epileptic discharge may be recorded not only in the suspected area but also in one or more other areas as well. The decision of which is the operative epileptogenic area, the choice between spike foci, can only be made on a concordance between EEG and clinical evidence—the aura—focal character of the fit. In yet other cases it is necessary to activate the brain with a convulsant and to watch the focal abnormalities in order to determine from which of them the seizure starts.

Intravenous metrazol, Megimide, chlorpromazine and other drugs are currently used for this purpose.

Subcortical type epileptic activity.—The third commonly encountered abnormality in the EEG is subcortical type epileptic activity. This phenomenon, the bilaterally synchronous episodes of spikes, spike and waves in different associations, has a number of forms. In its 3 c/s spike and wave form it was formerly regarded as the best EEG evidence of idiopathic epilepsy. Occasionally, however, this can develop after brain damage causing epilepsy and a cortical spike focus may also be present.

In the less characteristic forms of fast and slow spike and wave complexes, the subcortical type discharges are found in association with a very large number of diffuse pathological processes and the clinical associations are equally varied and do not necessarily include epilepsy (Hill, 1956). It seems very probable that these discharges reflect changed excitability in subcortical-cortical systems and in themselves have no pathological or diagnostic significance. They are observed in the EEGs of patients with many and varied neurological disorders, in epileptics, in catatonic schizophrenics, and in behaviour problem patients; there is no single symptom or grouping of symptoms that can be related to the phenomenon.

The EEGs of the two following patients illustrate disturbances in cortico-cortical and subcortical-cortical systems brought about in one patient by a meningioma—itself not localizable directly by the EEG, and in the other patient by a vascular disorder, a carotid artery thrombosis, whose effect might be expected to disturb the functions of one hemisphere predominantly.

Case I.—This woman aged 59, under the care of Mr. Murray Falconer, was found to have a large tentorial meningioma growing from the dura in the region of the anterior part of the right lateral sinus. The tumour had bulged up and invaginated the inferior part of the temporal lobe at the temporo-occipital junction. For seven years she had suffered from temporal lobe seizures with tinnitus and flashing red lights as an aura. On one occasion she had had an olfactory hallucination. There were no signs or symptoms of raised intracranial pressure. The EEGs showed: (1) An alpha rhythm which was *larger on the right side;* (2) rhythmic 2–3 c/s activity in the right frontal areas; (3) a focus of low voltage 6 c/s activity in the right central areas in the transverse electrode line; (4) very poor photic responses in the right parietal areas compared with those on the left; (5) gross reduction of barbiturate-induced fast rhythm in all areas, including the sphenoidal area, on the right side. After removal of the meningioma, *reduction* of the alpha rhythm was seen on the right side.

Case II.—This man of 47, under the care of Dr. Denis Leigh, was found to have partial occlusion of the right internal carotid artery from an atheromatous plaque. He had suffered three small "strokes" causing left-sided weakness, from which he recovered rapidly on the first two occasions. The third occasion resulted in coma and during recovery from this a left-sided Jacksonian fit occurred. He showed a left hemiparesis and left-sided astereognosis and autotopagnosia. This patient subsequently had an operation for removal of the atheromatous plaque and artery repair carried out by Professor C. G. Rob at St. Mary's Hospital. A series of EEGs showed the following characters:

(1) A reduction in the alpha amplitude on the right side together with poor responses to photic stimulation on this side (Fig. 1).

(2) Focus of rhythmic high voltage 2 c/s activity in the right frontal areas and low voltage 6 c/s activity in the right temporal areas (Figs. 2 and 3).

(3) Bursts of subcortical type epileptic activity, i.e. bilateral, mainly frontal grouped spikes and slow waves (Fig. 2).

(4) Under I.V. Pentothal narcosis, barbiturate fast rhythm showed gross reduction throughout *all* areas on the right side (Fig. 3).

(5) A focus of "sharp" waves at the right sphenoidal electrode, which persisted under Pentothal narcosis (Fig. 4).

Three months after operation the Pentothal pattern and the focus at the right sphenoidal electrode were still evident.

Discussion.—Any general statement about the diagnostic value of the EEG must include the recognition that the single routine EEG has a very limited value. At most it can provide an indication that something is wrong and perhaps roughly where it is wrong, but precisely what is wrong it cannot predict. In many patients the single routine EEG is normal, but if repeated studies are made in which the brain is subjected to activating measures and to a changed physio-chemical milieu, new information often becomes available which can throw light on the disturbed cerebral functions of the patient. For lack of a general theory we can again only use this information in an empirical way. It seems likely therefore that the use of the EEG as a single standardized test will be superseded in time by a series of detailed special investigations, planned in advance to answer certain quite specific questions about the cerebral functioning of the patient. Clinical diagnosis in terms of the anatomico-pathological concepts of disease, is, I suggest, at one remove from the data of the EEG. Hitherto we have not known precisely what questions to ask. If we knew them we might find that the answers to them are of an importance equal to those we get from other sources and by other methods.

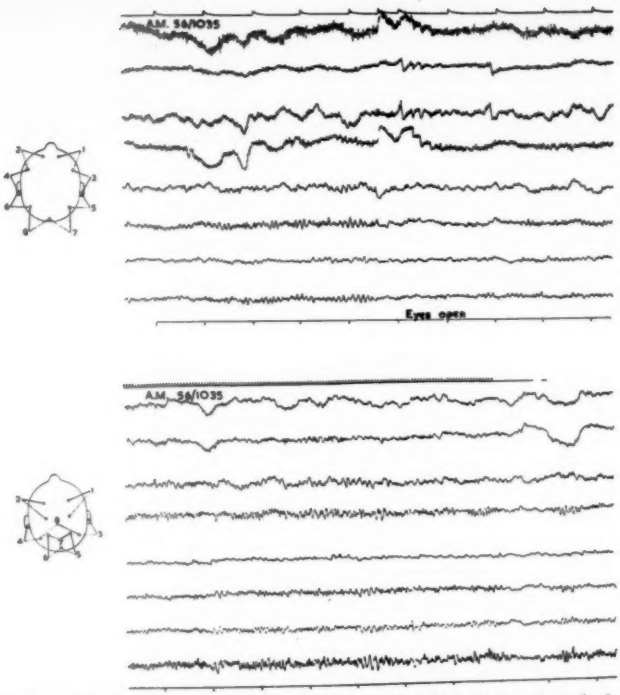


FIG. 1.—*Above:* Reduction in the alpha rhythm on the right side in channels 5 and 7 compared with the alpha rhythm on the left side in channels 6 and 8. *Below:* Reduction in the responses to photic stimulation seen on the right side in channels 3 and 5 compared with those on the left in channels 4 and 6.

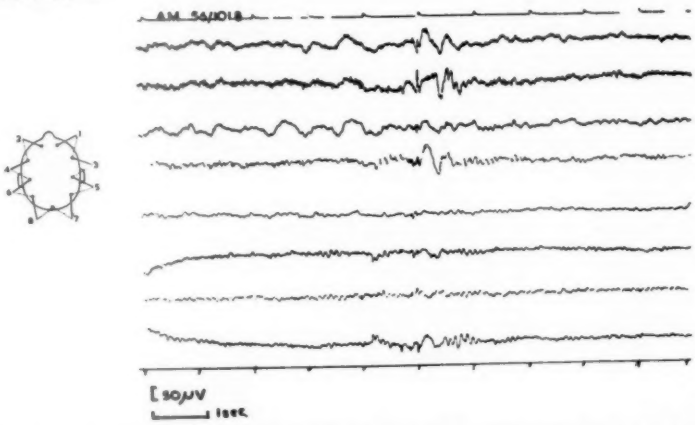


FIG. 2.—A burst of subcortical type epileptic activity: spikes and slow waves seen in the frontal areas maximally (channels 1–4) but also in all areas as spike discharges.

The new approach to the subject calls for some new attitudes and for significant changes in the practice of the subject. Comparatively few patients would be examined, but these would be examined repeatedly under a variety of conditions. This would call for a much closer working relationship between clinician and laboratory worker, both of whom must understand the clinical problem and the range of questions to which the EEG can provide

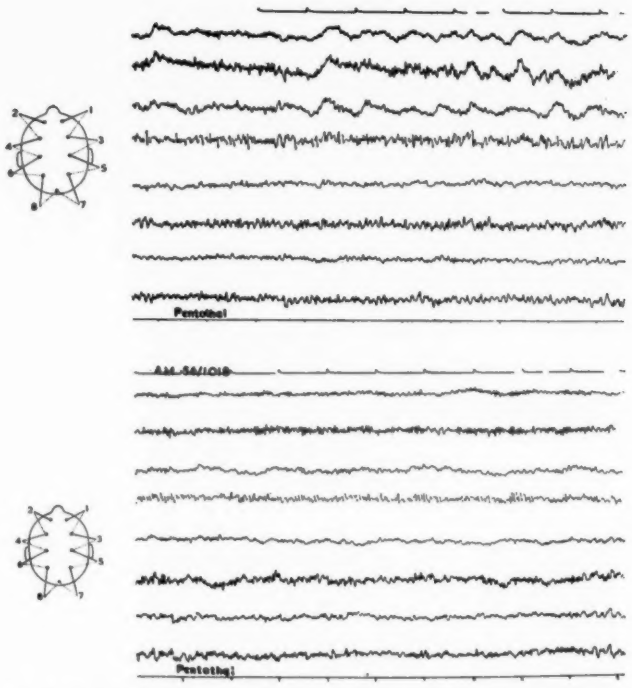


FIG. 3.—Records taken under intravenous Pentothal, showing reduction of barbiturate induced fast rhythm in all areas on the right side (channels 1, 3, 5 and 7).

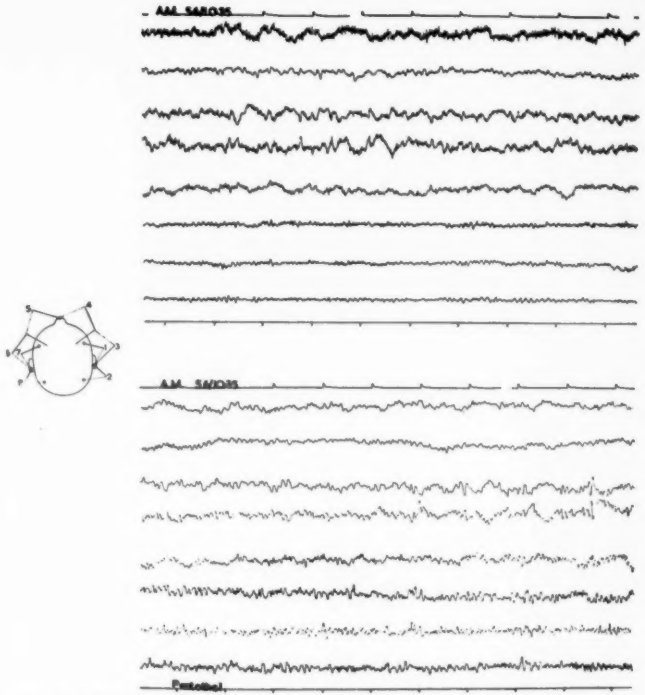


FIG. 4.—Records taken using sphenoidal electrodes showing (above) a focus of sharp waves at the right sphenoidal electrode (channels 3–4) with patient awake, persisting (below) under Pentothal narcosis.

any sort of answer. The isolation of the EEG laboratory and the lack of communication of ideas between clinicians and EEG workers in this country contrasts most vividly with the position in other countries. On the other hand there has been our failure to interest neurophysiologists in our problems. This again contrasts to our disfavour with other countries where we witness clinicians, physiologists and clinical EEG workers actively in communication and working together on clinical problems. Clinical electroencephalography may not yet have much importance in the whole field of the brain sciences. Yet in a sense the health and vitality of this small subject in any place, is a good indicator of one thing—the extent to which neurological thinking is based upon neurophysiological ideas and knowledge.

ACKNOWLEDGMENTS

I wish to thank Mr. Murray Falconer, Mr. Peter Schurr and Dr. Denis Leigh for their collaboration and for permission to report upon their cases. I am indebted particularly to Mr. Falconer for his interest and help in the planning of the EEG investigations and to Dr. W. A. Kennedy for his valuable assistance in carrying them out.

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Dr. Gerald Parsons-Smith (West End Hospital for Neurology and West London Hospital):

An entirely fresh dimension in neurology has been opened up by the use of serial EEG records instead of placing reliance upon single tracings. Records taken at regular intervals have proved of prognostic value in cases of head injury, epilepsy and in cerebral infections. They have a diagnostic value in differentiating between an improving vascular episode and a worsening neoplastic process. They have disclosed new facts; thus Cobb and Hill (1950) described the development of unique and diagnostic changes in subacute progressive encephalitis, whilst Gibbs and Gibbs (1947) found in other forms of encephalitis that children, unlike adults, develop 3 c/s spike and wave complexes in the course of the illness. In *cerebral lipidosis*, Cobb *et al.* (1952) found a remarkable diagnostic and persistent EEG pattern in children, but which does not occur in adults.

Although the EEG can be expected to give exact localization in about 70% of the gliomata and lateralization in 90%, it should not be employed to demarcate the anatomical limits of a *cerebral tumour* since this can be achieved so accurately by various radiological methods. Its value lies in the selection of cases for investigation and once they have been diagnosed to reinforce the clinical evidence of their progress. Indeed, in the course of such cases, the EEG tracings may show deterioration well before there is any clinical evidence of this. Differential tumour pathology is impossible on EEG grounds alone except when there are multiple focal abnormalities such as are seen with metastatic deposits. If the clinical and radiological appearances of the tumour suggest that it is a *meningioma* a persistently normal EEG indicates that it is avascular whilst it can be inferred from a severe focal abnormality that the tumour has developed a fringe of blood vessels from the internal carotid tree and will be extremely vascular at operation.

In *epilepsy* the pattern of the migration of foci in children was found after study of serial recordings. The work by Gibbs *et al.* (1954) throws most light on these changes. During the first year of life, generalized continuous epileptic discharges are frequently encountered in a pattern which they term hypsarrhythmia. This appears to be the most malignant form of epilepsy. Afterwards until about the age of 5, the picture is commonly one of impure epileptic complexes, mixtures of slow spikes and slow waves. From then until about the age of 12 generalized 3 c/s spike and wave discharges occurring in bursts are common and indicate a relatively benign form of epilepsy. Although these epileptic features are more or less specific for their age groups, they do not tend to be transformed from one to another with increasing age. During adolescence, generalized seizure activity becomes rare and anterior temporal discharges are more likely to be encountered. Focal epilepsy is seen, however, in young children when the occipital lobes are generally involved. If these cases are kept under observation, the epilepsy will either clear up completely or the foci will move forwards into the mid-temporal area. Around adolescence these, too, clear up or migrate into the anterior parts of the temporal lobes. They later migrate to deeper structures. In a series of children nearly half (48%) with occipital foci had become quite normal by the age of 9, whilst similar improvement later was found in those with mid-temporal lobe epilepsy, 50% having become normal by the age of 15.

Epileptic spike and wave activity is now known to occur in a number of different *biochemical disturbances*, though there may well be an underlying linkage between them

These rhythms have followed the prescription of one of the *hydrazides* which can induce a temporary epileptic state in animals and have been used to produce therapeutic convulsions. The most effective is thiocarbohydrazide, an oral dose of from 100 to 200 mg., producing a spontaneous seizure after one to three hours. EEG studies indicate that the seizures originate subcortically and 3 c/s spike and wave bursts have been recorded (Pfeiffer *et al.*, 1956). The epileptic response to these hydrazides is thought to be due to acute pyridoxine (vitamin B_6) deficiency, the most convincing reason being that when given by mouth it acts as a complete antidote to the temporary epileptic state.

Following experimental work on animals on synthetic diet and particularly Swank and Jasper's (1942) finding that epileptic paroxysms occurred in the EEGs of pigeons on a thiamine-deficient diet, Fox and Tulledge (1946) treated eight schoolboys of 14 and 15 years of age suffering from epilepsy with pyridoxine without the slightest change in the incidence of their fits. A similar clinical experiment was carried out by Livingston *et al.* (1955) who were not able to control epileptic seizures in any one of 31 patients treated with this substance. All these patients were over 6 months of age.

Experience with infants under the age of 6 months is, however, quite different. An outbreak of convulsive seizures occurred all over the U.S.A. and was reported by Coursin (1954) and Molony and Parmelee (1954). The common factor to these infants was the very pure dried milk preparation which was shown to be deficient in vitamin B_6. 54 of Coursin's cases responded immediately to treatment with pyridoxine as did Bickford's case (1954) whose EEG had shown hypsarrhythmia. Williams' case (1954) was controlled with this substance, but the fits recurred whenever it was deprived of it. 2–3 c/s spike and wave epileptic discharges occurred in the infant studied by Hunt *et al.* (1954) and these were abolished in the EEG fifteen minutes after the prescription of 6 mg. of pyridoxine. The infant's mother, in this latter case, had been given large doses of pyridoxine during pregnancy to control hyperemesis and it seems possible that in susceptible cases the fœtus develops an active enzyme system which is capable of accelerating the breakdown of pyridoxine. Following delivery, this metabolic anomaly could be manifested as a state of pyridoxine dependency in the infant.

It is interesting to compare this work with the changes described by Walton *et al.* (1954) in *pernicious anæmia* and vitamin B_{12} deficiency.

A high incidence of seizure activity of the *petit mal* type has been described in cases of *phenylpyruvic oligophrenia*, the 3 c/s spike and wave activity appearing particularly in sleep. The clinical picture of intellectual defect, muscular hypertonicity and occasional fits results from an inability to oxidize phenylalanine to tyrosine—and has been considered to be due to phenylalanine poisoning. The urine contains phenylpyruvic acid, phenylalanine and phenylacetic acid. No consistent pathological findings have been reported though in one case described by Corsellis (1953) one occipital lobe was demyelinated. Clinical improvement has been reported from several centres with phenylalanine-free diet but symptoms returned when a normal diet was substituted. In two of three typically fair-haired children so treated by Woolf *et al.* (1955) the *petit mal* ceased as did the spike and wave activity, the EEG becoming normal in one.

A new inborn error of metabolism has recently been described by Baron *et al.* (1956) and termed "*H*" *disease*. A defect in tryptophane metabolism to nicotinic acid has been postulated as the cause. They describe a family many of whom had a unique amino-aciduria.

Two of the children affected were subjected to serial EEG studies. The elder, a boy of 12, was mentally backward and developed in 1951 a pellagra-like illness with ataxia. He was admitted to the Middlesex Hospital under Dr. Edward Hart because these symptoms had not responded to vitamin-B therapy which had benefited his elder sister fourteen years earlier when she was similarly affected. Clinical examination disclosed a variable cerebellar syndrome together with some pyramidal involvement. The urine contained a variable amount of amino-nitrogen, from 600 mg. to 1,130 mg. per twenty-four hours, the normal figure being 41 mg. Paper chromatography disclosed a gross amino-aciduria. The urine contained at least twelve amino acids including analine, phenylalanine and tryptophane. A pyruvate-metabolism test was normal.

The disease was in an active phase during the period of EEG study. He was not drowsy. A feature of the tracings was the appearance of migrating 3 c/s focal abnormalities appearing over one or other of the temporal lobes. Thus, on 8.6.51 (Fig. 1) a severe 3 c/s abnormality was present in the left temporal lobe with a phase reversal. On 2.7.51 the dominant frequency was at 3 c/s and this occurred in all areas. A similar record was obtained three days later, but on 9.7.51 (Fig. 2) a 4 c/s focal abnormality was seen over the posterior part of the right temporal lobe, again with phase reversal. Three days later, this focal change disappeared. On 16.7.51 (Fig. 3) the 3 c/s focal change had reappeared over the left temporal lobe whilst three days later (Fig. 4) the focus had reappeared over the right temporal lobe. In the following month, there was a phase reversal over the right temporal lobe. In January 1952 the records were quite normal.

No further EEG examinations have been recorded, but he later developed violent outbursts of temper and developed choreiform movements. The symptoms continued to vary and one relapse

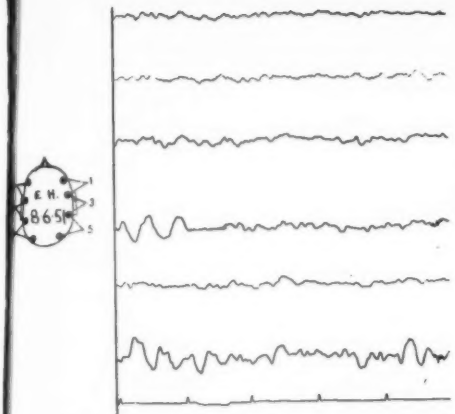


FIG. 1.—3 c/s focal abnormality over posterior part of the left temporal lobe.

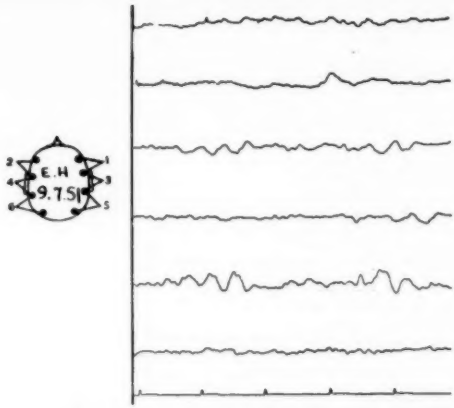


FIG. 2.—4 c/s focal abnormality over posterior part of right temporal lobe.

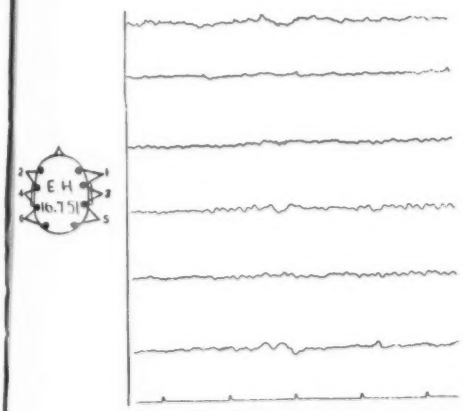


FIG. 3.—3 c/s focal abnormality over left temporal lobe.

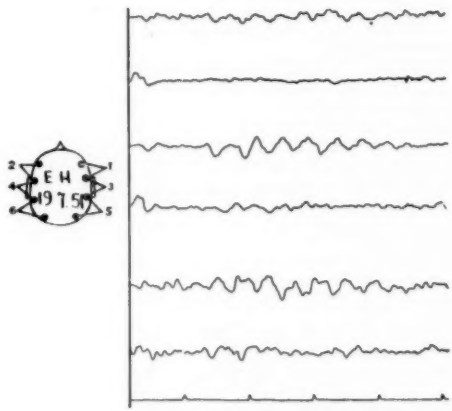


FIG. 4.—Focal abnormality over posterior part of right temporal lobe.

in 1955 was improved with chlortetracycline and nicotinamide. One of the patient's younger brothers also suffered from the amino-aciduria and rash, and was of low intelligence. His EEGs were similar to those of his brother, and in one a severe 3 c/s focal abnormality with a phase reversal was found over the right temporal lobe. His condition later deteriorated. In 3 other siblings normal EEGs were obtained. In 2 of these, the urine was quite normal, but the third, aged 6, showed the characteristic amino-aciduria though nothing clinically was amiss.

Reversible EEG changes dependent upon a disorder of protein metabolism are encountered in *portal systemic encephalopathy*. This condition is generally subsequent upon cirrhosis of the liver and the subsequent development of a portal collateral circulation. As a result, toxic nitrogenous material from protein breakdown in the gut avoids deamination, is deflected into the systemic circulation and adversely affects the brain, producing a picture of mixed pyramidal and extra-pyramidal disease which sometimes superficially resembles Parkinson's disease. The patients exhibit a flapping tremor together with changes in personality, confusional attacks, epileptic fits and sometimes even progress to psychotic states including mania and paranoia. These symptoms are always aggravated by increased nitrogen intake and coma may ensue. (Sherlock *et al.*, 1956.)

EEG studies have been carried out on 75 patients under the care of Drs. S. Sherlock, W. H. J. Summerskill and A. M. Dawson.

The results have been striking. The EEG tracings were placed into Grades 1 to 5, whilst the clinical condition was assessed in one of four grades. In the EEG, Grades 1 and 2 consisted of mild non-specific changes. In Grade 3, an alpha rhythm still appeared, but was disturbed by long runs of 5–6 c/s waves, whilst in Grade 4 no normal activity was seen, the dominant frequency being at 5–6 c/s in all areas. In Grade 5, this 5–6 c/s activity was disturbed by frontally-preponderant bursts of 2 c/s rhythms. The clinical grades were Grade 1, in which the changes were very mild, and Grade 2 when the flapping tremor was seen and there were early mental changes. In Grade 3, there was gross mental disorder with disorientation, whilst the patients in Grade 4 were stuporous. A close correlation was shown between the clinical state and the severity of the EEG abnormalities. The degree of the EEG abnormality was correlated with the level of ammonium concentration in the arterial blood, the peripheral vein blood and the C.S.F. Although the findings in most cases were striking, some discrepancies occurred which are being studied.

It has proved possible to reverse the EEG abnormalities by employing the specific treatment devised by Sherlock and her co-workers. If protein and nitrogen-containing drugs are completely withdrawn, whilst purges and chlortetracycline are given by mouth to diminish the small gut flora which act on the breakdown of protein and so assist in reducing the absorption of toxic nitrogen products, a quite normal EEG tracing may be produced coincidentally with the patient's clinical improvement.

ACKNOWLEDGMENT

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Dr. J. A. V. Bates (Neurological Research Unit (M.R.C.), National Hospital, Queen Square, London):

A single EEG will occasionally localize intracerebral disease when no clues to the localization are provided by thorough clinical examination and X-ray study. Usually this is known in retrospect when the disease has progressed to give other signs of its presence. But these cases emphasize the need to make the electrical evidence of intracerebral disease as firm and unequivocal as a quadrantic field defect, a yellow C.S.F., or a shift of the ventricular system. Alongside these cases of successful prediction by the EEG one could place many failures, for there are a number of pitfalls in the interpretation of abnormal electrical patterns obtained from a single routine scalp record. For example, it is now clear that localized

electrical abnormality may arise from histologically and functionally normal cortex which is being influenced only by nervous conduction from a remote area—in other words, that false localizing signs occur in the EEG just as they do in clinical neurology; that a record normal to-day may be abnormal to-morrow or with one type of abnormality to-day there may be a different type to-morrow; that an abnormality in a resting record may disappear during a fit, or alternatively during a fit may shift to a distant area; that clinical improvement is not necessarily related to electrical improvement and vice versa; and that as experience increases, inspection of an EEG record makes one less and less definite about inferring the state of consciousness of the patient, for considerable changes may occur in the level of consciousness with no corresponding changes in the scalp record and vice versa.

I think it is fair to say that the general trend of work on the exposed brain with large and small electrodes is to increase our wonder that the scalp record is of any use under any circumstances at all, for this work repeatedly reminds us of the highly localized nature of many types of electrical change and we must conclude that much electrical activity of clinical significance finds no representation at all in the scalp record. Nevertheless it is possible sometimes not only to obtain a localization of electrical abnormality on the scalp, but to get from the EEG presumptive evidence of local disease strong enough to justify a craniotomy when the patient is sufficiently disabled. This is illustrated by the following two cases.

Case I.—As a boy of 11 the patient was taken to hospital because for one month he had been having frequent short spells in which he lost consciousness but did not fall. An EEG showed a left temporal slow wave but there was nothing clinically to support the idea of local disease, X-rays were negative and the boy was given Tridione. This *petit mal* type of attack without any warning became more frequent and an occasional *grand mal* attack was added. He became surly and violent at times, drugs were changed, schooling became impossible, and he was sent to a colony. In the colony his behaviour was deplorable, his fits frequent and he was discharged at the age of 15 to a most unsatisfactory home. He first came to Mr. I. McCaul at the Whittington Hospital at the age of 19. He was a miserable specimen, sour and aggressive in between his fits, quite unemployable, in trouble with police and neighbours. He had no lateralizing aura to his fits, but he had a feeling that the ceiling was descending on him before he lost consciousness. He had no physical signs and A.E.G. and angiography were normal. In the EEG there was a well-localized left temporal sharp and slow wave abnormality, but a bilateral abnormality was frequently present also. We decided not to operate on his left temporal lobe because the EEG localization was not supported by any clinical or radiological evidence, and in view of his general personality and bilateral EEG disturbance we thought him a bad bet. His response to this decision was to attempt suicide by swallowing a large collection of tablets. His life was saved by a lucky chance, but he told us on recovery that he would do it again and not fail if he could not have the operation. Faced with this unusual predicament his left temporal lobe was explored with electrocorticography under local anæsthetic. The cortex looked normal but beneath the electrical focus a cyst 1 cm. in diameter surrounded by extensive gliosis was found and removed. Since the operation two years ago he has been entirely free from fits, though he has had an occasional "feeling" which does not develop further. There has been a striking change for the better in his general morale and behaviour and he is now at work for the first time in his life.

Case II.—A boy of 14 came under the care of Dr. Denis Williams. He was a normal child in a good home until at the age of 7 he had a series of major attacks. Anticonvulsants were given but the attacks continued without any localizing features and there was a sudden onset of severe aggressive behaviour associated with his attacks. He was investigated a year later. There was nothing to find clinically or on lumbar encephalography, but a single routine EEG reported on by Dr. W. Cobb showed a left frontotemporal slow spike and wave. This was suggestive of an acquired lesion but there was nothing to support it, operation was deferred and the boy was lost sight of. He, in fact, went from bad to worse, a colony could not keep him because of his severe behaviour disturbance and at the age of only 12 he was sent to an adult mental institution. Here he developed a left foot-drop and now, aged 14, was sent again to the National Hospital. Here he would have outbursts of extreme, aggressive behaviour terminating in a *grand mal* attack. The reason for his foot-drop was a mystery, but there was nothing to suggest an intracerebral lesion; a lumbar encephalogram was again normal. The most conspicuous feature of his very abnormal resting EEG was frequent bilateral outbursts of complex and irregular spike and wave episodes. They were most prominent in the frontal leads and showed a slight difference on the two sides of the head—the spikes were sharper and greater in amplitude on the right side and the slow components occasionally more marked on the left. It was suggested that there might be a left frontal lesion giving rise to secondary bilateral synchrony, but a left carotid arteriogram was reported on as normal. In spite of this further EEG explorations were done, for a significant piece of past history was now discovered, namely that after one series of attacks several years before he had had a dysphasia and right-sided weakness of a few hours' duration. In the further EEG tests there were several recordings from additional scalp electrodes, while intravenous barbiturates were given, and finally extradural electrodes were placed over each frontal lobe through frontal burr holes. These additional tests greatly strengthened the electrical evidence for a left frontal lesion and when a flap was turned by Mr. W. McKissock a large lesion was at once apparent. The operation notes read "the surface of the cortex shows an oval area of old haemorrhage, 5 cm. in diameter, greenish-yellow in colour and to me exactly the sort of lesion that one sees from intracranial hæmorrhage due to a cortical angioma. The area of abnormal tissue

extended down to the base of the anterior fossa and on to the undersurface of the frontal lobe extending as far backward as 1 cm. short of the lesser wing of the sphenoid". The electrical abnormality was even more widespread on electrocorticography and an extensive amputation of the left frontal lobe was performed. The pathologist reported that "sectioning was difficult owing to calcification but the specimen contained a cyst and locules of altered blood bounded by dense white connective tissue suggestive of an angiomatous malformation". The boy has been entirely free from fits since the day of operation over two and a half years ago and attends a normal school and is a socially satisfactory person.

Discussion.—These two cases bring out a number of significant points. First that in their fully-developed state both cases satisfy all the criteria on which "idiopathic epilepsy" is diagnosed: no localizing features in the character of the fit, no physical signs, special X-rays normal, generalized bilateral EEG disturbances; and they remind us that *grand mal* and a type of minor attack without lateralizing aura are common symptoms of local disease in a cerebral hemisphere. This point needs stressing because there is a tendency to look on fits of these types as evidence of a primary disorder of a "centrencephalic" system and *ipso facto* untreatable save by drugs. No EEG record should, in my opinion, ever be used to support a diagnosis of "idiopathic" or "essential" or "centrencephalic" epilepsy. These terms are, at the moment, required to cover our ignorance, and I would suggest that the EEG is being over-interpreted if it is used to make these terms scientifically respectable.

A second and more fundamental point which these cases illustrate is well known to electroencephalographers, namely the questionable value of a single routine scalp record. If it gives some supporting evidence, however weak, to a clinical impression, it may be appreciated, but if a localization is suggested for which there is no other support, the single routine scalp record will be ignored (and in my opinion rightly) because the evidence it provides is insufficiently definite.

It would seem that cases like the above two in which this occurs should be admitted to hospital for a thorough investigation of cerebral function with a series of electrical tests appropriate to the case planned by a clinician with special training in EEG methods and with neurosurgical assistance at hand. He will have a number of questions to consider: Shall medication be withdrawn? Shall a fit be provoked with an intravenous drug during a recording? Shall intravenous barbiturates be used? Shall sphenoidal electrodes be used, or shall electrodes be inserted through burr holes in the scalp? Is electrocorticography necessary? And so on.

As the variety of procedures and tests is multiplied and evidence of cerebral damage becomes consistent throughout different types of test, the EEG evidence has a chance of acquiring the necessary firmness, and only then will action be taken on it. There are good grounds for suspecting that the single routine EEG as at present conceived is strangling the proper development of the art. For the few trained people are occupied in the provision of a large volume of reports, many of which must be too indefinite to be helpful to the clinician, and, at worst, may be definitely misleading to him.

Section of Comparative Medicine

President—DOUGLAS MCCLEAN, M.B., M.R.C.S.

[*May* 15, 1957]

DISCUSSION: RECENT ADVANCES IN THE USE OF TISSUE CULTURE METHODS IN VIRUS RESEARCH

Dr. F. Kingsley Sanders:

Virus Titration in Cell Suspension Cultures

The behaviour of viruses within their host cells can best be studied under conditions where a known number of uniformly susceptible cells is exposed simultaneously to a known number of infectious virus particles, and the resulting yields of new virus accurately measured. This is most easily done when both cells and virus can be kept continuously in suspension, and is, in fact, standard practice in work with bacteriophages. Cell suspension cultures, however, have been little used in animal virology so far. Sanders (1953) described the multiplication of mouse encephalomyelitis virus in suspensions of mouse ascites tumour cells; later, Pereira (1954), and Dulbecco and Vogt (1954), studied the multiplication of fowl plague and Western equine encephalomyelitis virus in suspensions of cells prepared by the trypsinization of chick embryos. In all 3 cases the cell suspensions were used only as a primary growth system for the virus. Estimates of virus content were made separately by other techniques such as hæmagglutination titrations, infectivity end-point estimations in tube cultures, or by plaque counting on monolayer tissue cultures.

The present paper describes a technique whereby the progress of infection in a cell suspension culture can be followed directly, and includes a method for estimating directly the quantity of virus present in such a culture.

Theoretical considerations.—If a suspension of free, separate, cells at a concentration of C cells/ml. is mixed with a virus suspension and adsorbs V virus particles/ml. from that suspension, the average multiplicity of infection m, is given by the expression:

$$m = \frac{V}{C} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

whence

$$V = m \times C \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2)$$

Moreover, the proportion of cells infected by 0, 1, 2, ...n virus particles will be given by the successive terms of the Poisson series. The first term of this series is:

$$P(O) = e^{-m} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$$

Thus, if we can determine P (O)—i.e. the proportion of uninfected cells in such a suspension, m can be read off directly from a table of exponential functions. Then, if the total concentration of susceptible cells is also known, the virus content can be determined from the expression (2) above. C may be found by directly counting the number of cells present per ml. of suspension. To determine m it is necessary to find some way of distinguishing infected and uninfected cells in the suspension.

A method of titration based upon these principles has been used to study the multiplication of encephalomyocarditis (EMC) virus, in suspensions of mouse ascites tumour cells (Krebs 2 carcinoma). A description of this method is presented in the hope that a similar technique may be useful to other workers, in particular those who are investigating systems in which the multiplication and the release of virus may not be accompanied by any clear cytopathic effect. Ascites tumours consist of a large population ($1–2 \times 10^8$ cells/ml. of exudate) of separate similar cells floating free in fluid in the mouse peritoneum and can easily be recovered, washed and suspended in suitable media. Hoskins and Sanders (1957) have shown that such cells, maintained as a sheet of cells adherent to the wall of the culture vessel, are able to support multiplication of encephalomyocarditis (EMC) virus with high virus yields, and the production of cytopathic change.

Cell suspension cultures.—Mice with well-developed ascites are killed, and the tumour cell containing exudate aspirated from the peritoneal cavity, and the cells washed free of ascitic fluid by centrifuging with phosphate buffered saline (PBS, Dulbecco and Vogt, 1954). Such cells can be maintained in suspension by the methods described by Earle *et al.* (1955) in a simple mixture of saline and glucose. The culture vessels used are 150 ml. Pyrex, flat-bottomed boiling flasks containing 10 ml. cell suspension. The cells are maintained in suspension by shaking on a Brunswick type shaker at a rotation speed of 1 r.p.s. at 37° C. When such cultures are set up at a concentration of up to 3×10^7 cells/ml. of culture fluid there is no significant loss of cells during seventy-two hours of incubation; on the other hand, no significant cell multiplication occurs during this time.

Detection of infected cells.—In the past, a number of *in vitro* methods have been used to distinguish between "viable" and "non-viable" cells in a given preparation of tumour cells. Among these is the method suggested by Schrek (1936), who showed that when a tumour cell suspension is treated with 0·05% aqueous eosin under controlled conditions, differential staining occurs, which is correlated with cell viability; only "dead" or injured cells are presumed to stain.

When freshly washed suspensions of Krebs-2 carcinoma cells are treated in this way less than 5% of the cells take up the stain (Hoskins *et al.*, 1956). This is so both for cells freshly removed from mice with ascites, and for cells which have been maintained in agitated fluid cultures for up to thirty-six hours. However, when cultures infected twenty-four hours previously with a large amount of EMC virus were similarly tested, over 95% of the cells stained with eosin. It was therefore suspected that the cell staining of infected cultures might be correlated with the growth and release of virus from infected cells. Fig. 1 shows

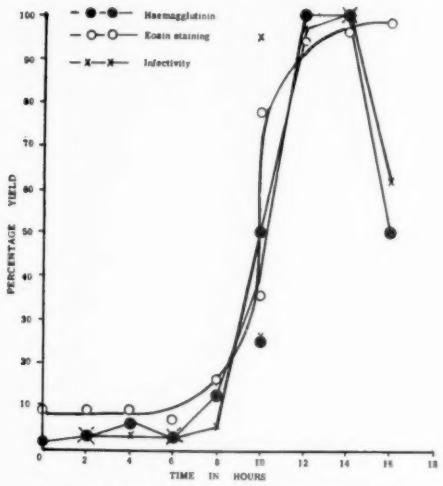


FIG. 1.—Coincidence between the time of release of EMC virus hæmagglutinin and the staining of infected cells.

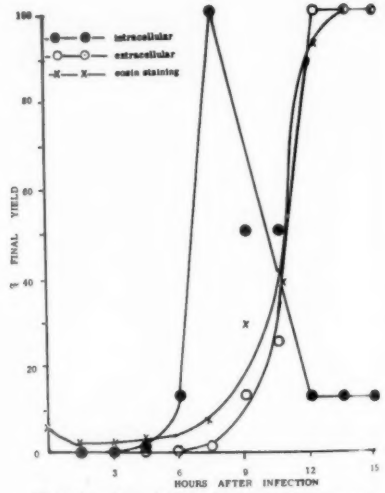


FIG. 2.—Correlation between the quantity of EMC virus released and the staining of the primary culture.

the percentage of cells taking up eosin in samples withdrawn from a suspension of tumour cells, at intervals after the addition of EMC virus in high multiplicity. It will be seen that there is a very close correspondence in time between the appearance of cell staining, and the virus content of the supernatant fluid of the culture. The figure also shows that the time before the release of new virus begins is of the order of eight hours, and that release of virus is virtually complete by fourteen hours. When suspensions of cells are infected at lower multiplicities, a smaller total number of the cells becomes stained. It is thus suggested that the staining reaction with eosin can be used to mark which cells in a given suspension have become infected. In each case a total cell count, together with a differential cell count of the cells remaining *unstained* by eosin (i.e. uninfected cells) provides all the information necessary to calculate the amount of virus adsorbed by the cells according to the principles given above. The basis of the test is to infect a suspension of cells with virus and after a time sufficient for one cycle of multiplication to take place (i.e. ten to fourteen

hours), to stain the cells with eosin, and count both the total number of cells and the proportion which remains unstained. From these figures the virus content of the suspension can be calculated. Fig. 2 shows the curve of virus release, when the virus content of the different suspensions is measured by this method, correlated with the results of hæmagglutination titrations of the same material, and with the appearance of eosin staining in the primary culture. It is seen that there is a very close agreement between the values obtained and the hæmagglutinin development curve. Such a method of titration has an accuracy close to that given by plaque counts, and about ten times the accuracy of end-point titrations in either tissue cultures or mice. For example: of two typical virus preparations, consisting of the supernatant fluid from infected suspension cultures, the first (K 9) has a titre of $1{\cdot}02 \pm 0{\cdot}08 \times 10^9$ cell-killing units/ml. (SE of the mean of 12 observations), the second (K 8) contained $1{\cdot}83 \pm 0{\cdot}08 \times 10^8$ cell-killing units/ml. (SE of mean of 11 observations).

In practice the time at which samples from the cultures are stained is critical. In experiments with multiplicities of less than 1·0, in which the course of the growth cycle was followed by means of the eosin staining reaction, clear evidence of a "second step" in the growth curve was found as early as fifteen hours after inoculation. To be certain that the proportion of stained cells found relates to only one cycle of growth, at least two successive samples should be counted between twelve and fourteen hours after inoculation; both should show roughly the same proportion of staining. Alternatively, sufficient encephalomyocarditis (EMC) antiserum to prevent the second cycle can be added to the culture one hour after infection. In this case it is advisable to use antiserum which has been adsorbed with cells to remove Krebs cell agglutination, otherwise clumping of cells in the culture may distort the results of the counts.

As a test of the validity of the method for measuring virus concentration a number of experiments were made in which virus and cells were mixed at different multiplicities and the proportion of unstained cells counted at eleven to fourteen hours after inoculation. The results are shown in Fig. 3.

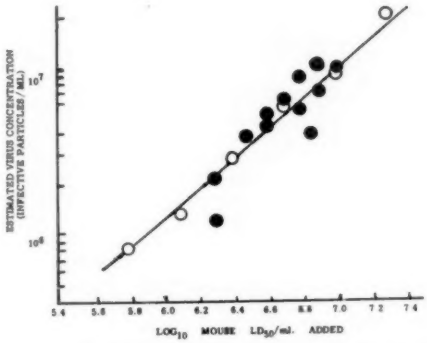


FIG. 3.—Comparison of virus titres obtained by the "cell-killing" method with those obtained in mice; explanation in text.

In the first experiment (shown by open circles in Fig. 3), a set of virus-cell mixtures were made in which twofold dilutions of virus were added to twofold dilutions of cells, the dilutions being chosen in each case to give an approximate multiplicity of 1·0 on the basis of the infectivity for mice of the virus suspension used. In the second experiment (shown by the black circles in Fig. 3) a constant cell concentration of 1×10^7 cells/ml. was infected with virus diluted so as to give multiplicities varying between 1 and 0·3. The amount of virus added, calculated from the known titres in mice of the virus suspension used, was then plotted against the apparent titre measured according to the principles described. The straight line is the calculated regression line for the whole data. This had a slope of 0·98 which was found not to differ significantly from the value of 1, which would be expected on theoretical grounds. It can, therefore, be concluded that the method, as used, provides a valid way of estimating the virus content of a suspension.

The method used at present for the performance of these titrations is as follows: Unknown virus suspensions are first titrated *in vitro* for their hæmagglutinin content. Once this is known the infective virus content of the suspension may be roughly estimated as

HA units/ml. $\times 10^6$. On this basis a cell suspension and virus suspension are prepared at such dilutions that when mixed they will give a theoretical multiplicity of between 0·1 and 1. The reason for the choice of this range is that at a multiplicity of one the suspension may be expected to contain about 37% of uninfected cells. At a higher multiplicity a smaller proportion of uninfected cells may be obscured by the presence of a small number of cells which are naturally resistant for some reason or other, i.e. although infected by virus they do not release new virus and thus do not stain. The preliminary hæmagglutinin titration is used merely as a guide to the correct virus and cell dilutions to choose for the actual titration itself.

At the lower end of the scale the method is not yet suitable for the measurement of small quantities of virus. The cells do not survive well at a concentration of less than 10^6/ml. and the proportion of stained cells at multiplicities of infection at below 0·1 are too small for accuracy in counting. Dilute normal uninfected tumour cell suspensions incubated for the same time as infected cultures may contain up to 10% of stained cells. Cells like this, which die a "normal" death, are likely to distort the results of cell staining titrations carried out with multiplicities of less than 0·1. Thus, the method as a whole cannot be expected to give reliable results when virus concentrations in the culture itself are less than 10^5/ml.

Comparison between the results of the cell-suspension and plaque titration methods.—A plaque method of titration for the system EMC virus/Krebs-2 carcinoma cells has recently become available and will be reported elsewhere. Fig. 4 shows the type of plaques obtained

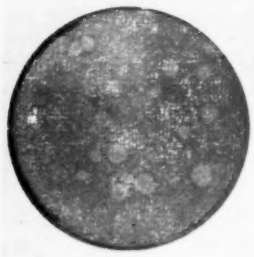


FIG. 4.—Plaques given by EMC virus (K 2 strain) on a layer of Krebs-2 carcinoma cells, stained with Neutral Red.

with this virus and the Krebs-2 carcinoma cells. When selected virus suspensions are titrated simultaneously by both methods the results obtained do not always closely correspond. Any differences observed can, however, be related to the nature of the virus suspension itself and not to the errors of the methods. For example, "fresh" virus—i.e. virus harvested and titrated immediately upon its release from infected cells—or "intracellular" virus—i.e. virus released artificially from infected cells by shaking with glass beads at the peak of the multiplication cycle—give the same virus content whether measured by plaque titration or by eosin staining in cell suspension cultures. However, virus which has been frozen and thawed in the absence of protective protein, or heated for more than one hour at 37° C. shows a much lower infectivity titre by plaque count than by the staining method. Similarly, fresh virus released from cells at very high multiplicities of infection also has a lower virus content when measured by the plaque method than by cell staining. In this connexion it must be remembered that a plaque forming particle represents a virus unit which is able to infect cells and multiply within them to form new virus which can then initiate further cycles of infection in other cells; and this process must go on long enough to produce a visible plaque. The cell staining procedure, on the other hand, measures virus which is able to adsorb to cells and initiate changes within them so that the infected cells are killed after a time equivalent to one growth cycle; no virus able to infect other cells need be released. It is obvious, therefore, that the cell staining and plaque methods of titration do not necessarily measure the same virus property. For this reason we now express the content of virus suspensions titrated by the cell staining method in cell-killing particles (CKPs) per ml., to distinguish this property from the plaque-forming particle (PFP) content of such suspensions. There is preliminary evidence that the CKP can appear as a degraded form of the PFP, and also that infection of cells at very high multiplicities can perhaps produce progeny virus where a great excess of CKPs are present. Generally speaking, the hæmagglutinin content of EMC virus suspensions follows its CKP and not its PFP content.

Further applications.—As with other titration methods the method can also be used to measure the antibody content of sera. In this way, incubated serum virus mixtures can

be added to a larger volume of cell suspension and the number of uninfected cells estimated. With appropriate experimental design the rate constant of neutralization (K) can be measured with fair accuracy.

General principles.—In order that similar methods can be applied to other cell virus systems the following conditions must be fulfilled:

(1) The cells used should be separate, identical, and capable of surviving in free suspension for the period of observation necessary without significant mortality.

(2) A high and constant proportion of the infecting virus present must rapidly adsorb to the cells and subsequently undergo "multiplication".

(3) A method must be available for distinguishing unequivocally between infected and uninfected cells, for measurement of the proportion of uninfected cells must be carried out after an interval sufficient for one growth cycle, and no more.

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Mr. R. F. Sellers:

Some Observations on the Plaque Technique

Since Dulbecco (1952) introduced the plaque technique, it has been successfully applied to a number of viruses (*see* Isaacs, 1957). Two methods are used. In one a cell monolayer grown on glass is infected with virus and covered with an agar or plasma overlay (Dulbecco, 1952; Noyes, 1953); in the other a suspension of cells is infected with virus, melted agar added, and the mixture poured on to a preset agar plate (Cooper, 1955). In both methods after a period of incubation the necrotic areas caused by the virus (the plaques) are brought into prominence by an intravital dye. The plaques can then be counted, measured or isolated as a pure virus clone.

In 1955 I found that the virus of foot-and-mouth disease multiplied on pig and calf kidney-cell monolayers and that plaques could be produced on pig kidney-cell monolayers (Sellers, 1955). Since then we have used these monolayers extensively. Cell suspensions obtained by trypsinization from the kidney cortex are grown in glass containers in a medium consisting of Earle's saline, lactalbumin hydrolysate 0·5%, yeast extract 0·01% and 7·5–10% ox serum. The cultures are incubated at 37° C. in an atmosphere of 4% CO_2 in humidified air. After six days' growth the monolayers formed are transferred to Petri dishes using a minimum cell concentration of 4×10^5 cells/ml. and incubated under the conditions described before. Complete monolayers are formed in two days, and are then infected with a suitable virus dilution and after an adsorption period of 30 minutes covered with an agar overlay. The agar overlay consists of 1·2 ml. 3% Difco washed agar in distilled water, 0·1 ml. neutral red in distilled water, 1·3 ml. twofold Earle's saline, 0·2 ml. ox serum and 0·9 ml. of Earle's saline, lactalbumin hydrolysate, yeast extract solution. The plaques may be seen and counted from two days onwards.

It is an essential requirement of the technique that the virus should destroy the cells, but several factors affect the cytopathic action, the virus yield and the number and morphology of the plaques formed. A monolayer culture normally susceptible to virus action may become resistant due to changed culture conditions. This resistance may be due to the presence or overgrowth of the susceptible cells by a resistant cell population or to a physiological change in the susceptible cells. In a study of the action of the virus of foot-and-mouth disease on calf kidney-cell monolayers, my colleagues Mrs. Burt and Miss Cumming (Burt, Cumming and Sellers, 1957) have found that by continued culture and infection in the presence of ox serum the cytopathic action of the virus on the epithelial type cells is masked by the overgrowth of a resistant fibroblastic type of cell. By reduction of the ox serum concentration and addition of pig serum, the rate of growth of the fibroblastic cells appears to be hindered, and in many instances plaques can be produced, which although smaller give a similar titre to those obtained on pig kidney-cell monolayers. Wesslén and Dinter (1956) have found a similar effect on calf kidney cells, when they used bovine amniotic fluid in the medium. My colleague Pay (1957) describes two types of cells encountered in monolayer cultures of adult cattle tongue epithelium, both of which produce virus but only one shows the cytopathic changes. Resistant fibroblastic-type cells are present to a certain extent in pig kidney cultures, but here culture conditions affect the

physiological state of the cells (Sellers, 1957). When the monolayers are grown in a medium, where Hank's saline is substituted for Earle's, among strains of the virus of foot-and-mouth disease forming large plaques the plaques are smaller and fewer and the cytopathic effect is reduced. When Earle's saline is used and excess carbon dioxide allowed to act on the cells for a short time, there may be a reduction of thirtyfold or more in the number of plaques formed on a plate, the plaques are smaller and in the case of strains forming small plaques may be absent altogether. Presumably it is the effect of pH on the cell metabolism which causes this; a high bicarbonate content buffered by a regular concentration of carbon dioxide being preferable. Gifford *et al.* (1956) found a decreased virus yield of polio virus from HeLa cells due to an increase in acidity, and Barron and Karzon (1957) described a pH effect on the cytopathogenicity of orphan viruses on monkey kidney tissue cultures. Sabin (1956) found a delayed cytopathogenic action and reduced yield of non-neuropathogenic strains of poliomyelitis virus in monkey kidney cultures under acid conditions.

Another factor affecting the culture is the state of the kidney from which the original cell suspensions are obtained. Under similar conditions we have noticed that cells from some kidneys grow faster and better than from others, and my colleague Sharpe (1957, personal communication) has recently demonstrated a difference in size and number of plaques formed by the virus of foot-and-mouth disease on monolayer cultures obtained from different pig kidneys. Dulbecco and Vogt (1954) found that slow growing testis cultures were less sensitive than the fast growing ones for the formation of plaques with poliomyelitis virus.

An essential requirement is that the monolayer be complete, and we have found that transferred monolayers are more satisfactory in this respect. A cell inoculum of minimum concentration of 4×10^5 cells/ml. is essential. In incomplete monolayers some of the virus may come into contact with glass and the rate of spread from the cell initially affected is reduced; in the complete monolayer cells closely packed survive better under the agar overlay.

The composition of the overlay has been found to affect the type and size of plaque. Dulbecco and Vogt (1955) have described a virus line, which produces large plaques under an overlay containing either embryo extract or monkey serum, whereas the wild type produces large plaques under the monkey serum overlay but small plaques under the embryo extract overlay. They have also found that certain mutants (d type) take longer to appear under an acid overlay than under a normal overlay, and that these mutants are non-pathogenic for the nervous system of monkeys (Dulbecco, 1957; Sabin, 1956). Rappaport (1956) has found that the number of plaques is increased when an amino-acid mixture is substituted for calf serum in a calf serum-Earle's saline overlay; and Dubes (1956) has found that plaque development is retarded when cystine is omitted from Eagle's maintenance medium in the overlay. Hsiung and Melnick (1957) have also described the effect of the overlay composition on the appearance of plaques. So far we have not investigated the effects of overlay of different composition on the formation of plaques by the virus of foot-and-mouth disease, and our overlay composition resembles that used in the growth of the cells. For the formation of plaques on calf kidney-cell monolayers a reduction of ox serum and addition of pig serum is beneficial (Burt, Cumming and Sellers, 1957).

It is clear that there are optimum culture conditions for each virus-host cell system, and departure from the optimum may lead to loss of sensitivity and reproducibility. The need for optimum cultural conditions is perhaps more necessary for kidney cultures, where the cells are cultivated *in vitro* for eight to fourteen days, than in chick embryo monolayers, where a monolayer is formed in twenty-four to forty-eight hours and the virus infection and plaque count completed in another three days. Pure cell lines derived from single cells (Puck, Marcus and Ciecura, 1956) which are adapted to *in vitro* conditions would be more suitable, but optimum conditions for them would still have to be determined.

Under the culture conditions described before most strains of the virus of foot-and-mouth disease examined show a linear relationship between virus dilution and number of plaques indicating that plaques are initiated from single virus particles.

Table I shows a good relationship in the case of strain M.11 pig kidney virus. With strain Ven. 1 derived from bovine tongue epithelial tissue cultures the relationship is not good. This strain produces small plaques on pig kidney-cell monolayers and titres of the same material in mice are higher. However when trypsinized bovine tongue cell suspensions (Cartwright, Pay and Henderson, 1957) are infected with virus, washed free of unadsorbed virus and tested on pig kidney-cell monolayers, then the relationship holds good and titres in mice are the same.

In a previous paper (Sellers, 1955) I said that the titres obtained by mouse inoculation and plaque count were in fair agreement. Further comparative titrations have been carried out and Tables II, III and IV show the results of such titrations. In some cases the mouse titre is higher, in some the same and in others lower than that obtained by plaque count. Titrations by other methods are included for comparison.

TABLE I.—RELATIONSHIP BETWEEN NUMBER OF PLAQUES AND CONCENTRATION OF VIRUS

	Relative concentration of virus	No. of plaques on each plate	Expected mean	Observed mean
Strain M.11	1	39, 42, 50	38	44
Pig kidney	$\frac{1}{2}$	12, 18, 18, 19	19	17
59th pass	$\frac{1}{4}$	9, 10, 10	9·5	9·7
Strain Ven. 1 ..	1	20, 30	55	25
Bovine tongue ..	1/10	7, 10	5·5	8·5
Epithelial culture ..	1/100	0, 0	0	0

TABLE II.—COMPARISON OF TITRES OBTAINED BY DIFFERENT METHODS OF TITRATION

		P.F.U.(*a*)	Mouse I.U.(*b*)	Cattle I.U.(*c*)
M.11	12th cattle pass ..	6·1	6·0	6·4
	58th pig kidney pass	6·3	7·4	6·2
	190th mouse pass ..	4·3	6·7	—

TABLE III.—COMPARISON OF TITRES OBTAINED BY DIFFERENT METHODS OF TITRATION

	P.F.U.	Mouse I.U.	Chick(*d*) embryo I.U.	Cattle tongue(*e*) epithelium Perspex plates I.U.	Cattle tongue(*f*) epithelium monolayers I.U.	Cattle I.U.
Ven. 1						
10th Cattle pass ..	6·6	7·7	—	—	—	6·3
99th Chick embryo pass	5·8	7·0	5·6	3·3	5·3	—

(*a*) Plaque forming units (Sellers, 1955). (*b*) Skinner (1951). (*c*) Henderson (1949).
(*d*) Skinner (1954). (*e*) Brooksby and Wardle (1954). (*f*) Pay (1957).

TABLE IV.—COMPARISON OF TITRES OBTAINED BY DIFFERENT METHODS OF TITRATION

		P.F.U.	Mouse I.U.
KEN/3/57	2nd pig kidney passage	5·8	5·7
	9th pig kidney passage	6·2	5·9
KEN/121/56	4th pig kidney passage	5·7	4
	5th pig kidney passage	5·3	3·8

The numbers in Tables II, III and IV represent the log. titre in infectious units per ml. assuming 1 ID50 = 0·7 I.U.

Differences between titres perhaps reflect the degree of adaptation to the host of the virus strain used. Important are the physiological state of the cells (as mentioned before) and deriving from this the physiological state of the small or large animal used for titration. Important too are the degree of adsorption and the extent to which the virus remains at the site of inoculation. When the monolayer plates are overlaid after the adsorption period, the fluid containing the unadsorbed virus is mixed with the overlay, and consequently the virus is subject to heat inactivation and other adverse conditions. With the virus of foot-and-mouth disease, washing the cells after varying periods of adsorption has shown that 60% of the final count has been subjected to this influence, so that the actual titre may be higher. When a three dimensional system such as the cell suspension method is used, a greater efficiency should be obtained, and Cooper (1955) has shown with the virus of vesicular stomatitis that in the cell suspension method 30–50% more plaques are obtained than by the monolayer method. My colleague Miss A. Cumming (1957, personal communication) with the virus of foot-and-mouth disease has found a higher titre using suspensions of calf kidney cells than with pig or calf kidney-cell monolayers. With strain Ven. 1 mentioned before the better relationship with the cell suspensions may be a result of better adsorption on to tongue epithelial cells due to the adaptation of the virus to them and to the fact that it is a three dimensional system.

Under the culture conditions described before use has been made of another advantage of the plaque technique, namely the isolation of pure virus clones and the use of plaque morphology as a genetic marker. With the virus of foot-and-mouth disease differences in plaque size and shape have been seen between and within strains. Large, medium and small plaques with well-defined or irregular edges have been observed (Sellers, 1957). In Fig. 1 can be seen large and medium plaques obtained with strain KEN/3/57 Type S.A.T.2, and in Fig. 2 smaller and irregular plaques with strain KEN/121/56 Type S.A.T.2. M.11 pig kidney strain produces large and medium regular plaques on pig kidney-cell monolayers,

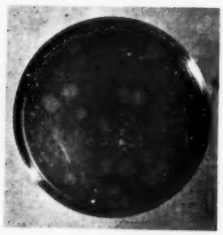


FIG. 1.—Plaques of the virus of foot-and-mouth disease strain KEN/3/57 on pig kidney monolayers forty-eight hours after infection.

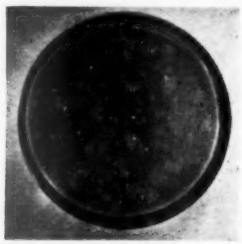


FIG. 2.—Plaques of the virus of foot-and-mouth disease strain KEN/121/56 on pig kidney monolayers forty-eight hours after infection.

while M.11 cattle strain produces small irregular plaques with an occasional larger one. Subculture from single plaques has been carried out with success.

The plaque technique is essentially a macroscopic study of virus-cell interaction. The information that can be obtained from each plate on which there are plaques is extensive. There is an accurate estimate of virus titre, a knowledge of plaque morphology, the possibility of isolating virus clones and indications of cell metabolism. The effects of culture conditions on cytopathogenicity, plaque titre and plaque morphology are important from the point of view of detection of infective virus in inactivated vaccines; this and the problem of adsorption might be overcome by incubating the virus with high concentrations of cells from different hosts and tissues before inoculation of the tissue culture or animal. By using different cell strains under different conditions it is possible to use the plaque technique as a means of differential diagnosis; by the same methods it may be possible to define the conditions necessary for growth, detection and isolation of virus mutants and variants non-pathogenic for the animal host; and these could be used as a live vaccine, as is being done with polio virus. (Dulbecco, 1957; Sabin, 1956). Conversely by the same methods virus strains may be isolated which are highly pathogenic and antigenic and which would be suitable for preparation as inactivated vaccines. With the plaque technique problems of cell physiology might be studied using a standard virus clone as a plaque marker and defining the conditions of the cells which produce variations in plaque size. The difference in titre by the different methods of virus assay raises the question of the ability of virus to adsorb on to cells, to penetrate cells, to multiply and produce characteristic changes in the host cell or organism. Again by varying cell strains and conditions, by varying virus types and strains it may be possible to obtain some knowledge of this problem, which could be applied at the organism level.

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Mr. T. W. F. Pay:

The Propagation of the Virus of Foot-and-Mouth Disease in Monolayer Cultures of Adult Bovine Tongue Epithelium

A survey of the literature has so far revealed few references to the growth on glass of monolayer tissue cultures prepared from trypsin dispersed cell suspensions of normal adult stratified squamous epithelium. This has been probably due very largely to the difficulty in obtaining a suitable source of such tissue in a sterile condition, and without admixture of other structures such as hair, glandular tissue, connective tissue, etc. The adult bovine tongue, however, does provide such a source of epithelium, and monolayer cultures can be grown from it without difficulty. Attempts to produce cultures of this type were first made principally to obtain a system more suitable than cell-suspension cultures of tongue epithelium (Cartwright *et al.*, 1957) for the study of certain aspects of virus multiplication. It was soon found, however, that the interpretation of results of "growth curve" experiments so obtained was complicated by the occurrence of two quite distinct types of cell growth, which behaved very differently following infection with foot-and-mouth disease virus.

Methods of preparation of tissue cultures.—Cattle tongues were obtained fresh from the abattoir. After washing, the superficial keratinized layer of the mucosa was removed by the traction method described by Frenkel (1947). The deeper layers of the stratum malpighii were then collected by slicing off with a sterile razor blade. This tissue was minced with scissors and placed into a sterile solution of 0·5% trypsin (Difco 1:250) in a calcium and magnesium free modified Tyrode solution (Rinaldini, 1954). It was then incubated at 37° C. for half to one hour, during which time it was agitated to assist separation of cells. The resulting cell suspension was filtered through a coarse mesh stainless steel gauze to remove large fragments of undigested tissue, and then allowed to stand for several minutes to sediment out the denser clumps of tissue, mainly the basal portions of filiform papillæ, which had passed through the filter. The decanted supernatant was centrifuged at 1,000 r.p.m. for 2 to 3 minutes, and the cell deposit resuspended in culture medium without washing. Several media have been employed, including bovine amniotic fluid + 10% bovine serum (BAF + BS); 0·5% lactalbumin hydrolysate in Tyrode solution + 10% bovine serum (LH + T + BS) and Tyrode solution + 10% bovine serum (T + BS).

Cytology of cultures.—Cell suspensions prepared in this way consisted of a mixture of single cells and cell clusters of varying sizes. Filtration and sedimentation procedures were directed towards including cell clusters only up to the order of 1 mm. diameter. Histological examination of sections made from centrifuged deposits of the suspensions showed that the majority of the clusters were bounded on one or more sides by basal layer cells, and hence probably were derived from fragments of the epidermal rete ridges.

When BAF + BS or LH + T + BS were employed as culture media, two distinct types of cell growth developed. Within twenty-four hours the cell clumps and single cells had adhered to the glass of the culture vessel, and usually after forty-eight hours evidence of cell growth was apparent. Around the cell clumps a zone of cells developed which formed an almost intact "membrane-like" sheet, whereas on those parts of the glass where only single cells were adherent, a growth of discrete polygonal-shaped cells developed.

The "membrane" type of cell growth was seen only in association with cell clusters. In living cultures, it was characterized by a somewhat refractile continuous sheet of cells in which some nuclei could be seen, but cell boundaries were difficult to recognize. Phase contrast microscopy, or a silver impregnation method of staining revealed the cell boundaries and demonstrated a typical mosaic "pavement-epithelium" type of arrangement (Fig. 1). Near to the cell clumps, the cells were often more than one layer deep and overlaid one another in an irregular fashion. So far it has not been possible to passage serially cells of this type.

The "polygonal" type of cell growth consisted of irregular polygonal-shaped cells with long cytoplasmic processes. Morphologically, they resembled HeLa or kidney cells in monolayer cultures, and even when cells had become tightly packed together it was always possible to recognize the discrete nature of the cells (Fig. 2). Cells of this type have been

successfully propagated in serial cultures and have been maintained in the original culture vessels for periods of at least six months.

When the cell suspensions were cultivated in T + BS it was found that only the "membrane" type of cell sheet developed. The single cells persisted on the glass without undergoing division. Table I shows the results of an experiment where duplicate "flying coverslip" preparations were incubated for four days in either LH + T + BS or in T + BS. Some were then left in the original media and some from each group, after washing, were transferred to either LH + T + BS + M/20,000 colchicine or to T + BS + M/20,000 colchicine, and incubated for a further eighteen hours. The coverslips were then fixed and stained. Table I indicates the relative amounts of growth and the mitotic index of each type of cell growth found in the various groups. These results suggested that T + BS would not support mitosis in either type of cell growth, whereas the addition of 0·5% w/v lactalbumin hydrolysate was sufficient to stimulate mitosis in either type of cell growth, the mitotic index for the "polygonal" cells being about twice that of the "membrane" cells. After four or five days' incubation in T + BS the cell sheets of the "membrane" type were almost as extensive as those produced in the more complete growth medium. Hence it appeared that this type of growth originated mainly by migration of cells from the original cell clusters.

TABLE I.—COMPARISON OF AMOUNT OF GROWTH AND MITOTIC ACTIVITY IN CELLS OF THE "MEMBRANE" AND "POLYGONAL" TYPES AFTER INCUBATION IN EITHER LH + T + BS or T + BS

Culture Medium		Membrane Cells Develop around cell clusters only		Polygonal Cells Develop from single cells	
4 days +	18 hours	Growth	Mitosis	Growth	Mitosis
LH + T + BS	LH + T + BS	+ + +	6/1000	+ + +	11/1000
LH + T + BS	LH + T + BS + colchicine	—	—	+ + +	60/1000
	T + BS + colchicine	+ + +	0/1000	+ + +	4/1000
T + BS	T + BS	+ +	0/1000	±	No mitosis
T + BS	LH + T + BS + colchicine	+ + +	22/1000	±	50/1000
	T + BS + colchicine	+ +	0/1000	±	No mitosis

Cytopathogenic effects.—Following infection with the virus of foot-and-mouth disease, the two types of cell growth responded in quite different ways. Both appeared to support the multiplication of virus. In the case of cells of the "membrane" type, this was accompanied by cytopathogenic effects leading to cell death; whereas young cultures of the "polygonal" type of cell showed little or no evidence of cytopathogenic effects. To make interpretation of the time sequence of the various stages of cell degeneration easier, experiments were made in which cultures were infected with large inocula of seed virus to produce initial infection of all susceptible cells. These cultures were then examined either in the living state by phase contrast microscopy and cine-photomicrography, or by microscopy of fixed and stained coverslip preparations. No significant differences in the nature of the cytopathogenic response, other than the time sequence, were observed in cultures infected with limiting dilutions of virus.

As early as three to four hours after infection, the membrane cell sheets began to retract and become fenestrated in appearance, and by four to five hours many cells had begun to produce large cytoplasmic protrusions (Fig. 3). These were usually radially arranged, starting as small hemispherical blebs and proceeding to long club-shaped or filamentous structures. They were never observed to burst or to become detached from the cell, but they appeared to coalesce gradually until they enveloped the cell. Thus by eighteen hours most of the cells took the form of large, clear spherical cells, which would seem to bear some resemblance to the cells showing hydropic degeneration found in the developing vesicle on the tongue or foot of an infected animal (Fig. 4). At this stage, the nuclei were completely pyknotic and by usual histological criteria the cells would have been presumed to be dead. However it was found that the majority of such cells were still impermeable to eosin, which readily stains dead cells. This is in keeping with the probable continued function of the cell membrane suggested by the swollen nature of the cells. Wesslén and Dinter (1956) have described similar cytopathogenic changes in plasma clot cultures of bovine embryonic tongue and skin epithelium infected with the virus of foot-and-mouth disease. Damaging the cells by heat or by exposure to hypotonic solutions produced cytoplasmic protrusions in cells of the "membrane" type. However, these protrusions remained hemispherical, usually numbered only 2 or 3 per cell, and never gave rise to the picture produced by virus infection.

Cultures consisting predominantly of the "membrane cell" type of growth have been

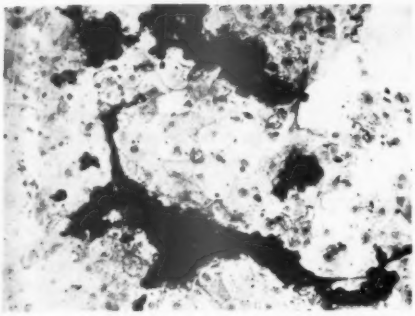


FIG. 1.—Cell clusters with "membrane" cells stained by silver impregnation to demonstrate cell boundaries. Three days' growth in T + BS. × 92.

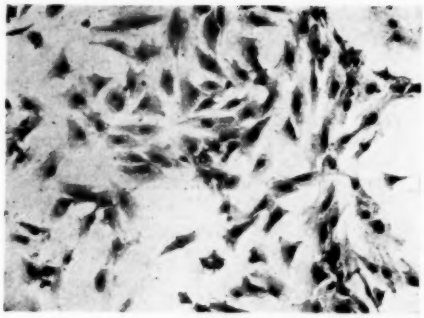


FIG. 2.—"Polygonal" cells. Five days' growth LH + T + BS. × 92.

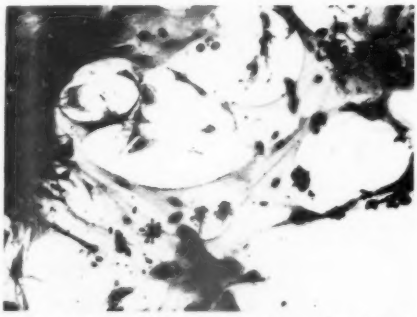


FIG. 3.—"Membrane" cell sheet, five hours after infection with large inoculum of foot-and-mouth disease virus, showing fenestration and cells with cytoplasmic protrusions. × 92.

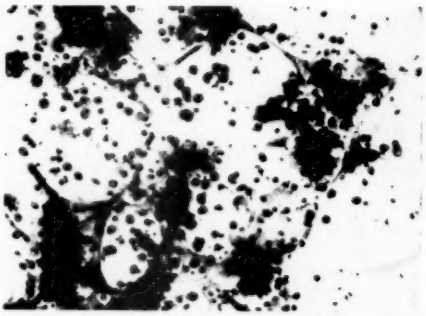


FIG. 4.—"Membrane" cell sheet, eighteen hours after infection with large inoculum of foot-and-mouth disease virus, showing almost complete destruction of cell sheet and swollen, spherical cells with pyknotic nuclei. × 92.

successfully used as a titration method, 50% end-points being calculated from numbers of cultures showing cytopathogenic changes after inoculation with dilutions of virus. Results obtained in this way have given close agreement to those obtained from the inoculation of unweaned mice or from plaque counts and limiting dilution methods in pig kidney-cell monolayer cultures.

Recently the observation has been made that a number of strains of foot-and-mouth disease virus that have been serially passaged in mice or in embryonated eggs, and have reached a stage of failing to produce vesicular lesions when inoculated into the tongues of susceptible cattle, also fail to produce cytopathogenic changes in cultures of tongue epithelium containing the susceptible "membrane" cell type growth. One of these strains has been shown to multiply in such cultures and to give virus yields comparable to those given by strains pathogenic for cattle.

Hence, to summarize the present position regarding the cytopathogenicity of strains of foot-and-mouth disease virus for tongue epithelial cell cultures, it appears that unadapted virus strains multiply in both "membrane" and "polygonal" type cells and produce cytopathogenic changes in the former only, some attenuated strains multiply in both types of cell and fail to produce cytopathogenic effects in either, and some other attenuated strains may fail to multiply at all in tongue epithelial cell cultures.

The results of a few experiments have so far suggested that the *Indiana C.* strain of vesicular stomatitis produces cytopathogenic effects in the "membrane" cell type of growth only, but probably multiplies in cells of both types.

Virus multiplication.—It will not be possible here to give any detailed account of the results of virus multiplication studies using tongue epithelium monolayer cultures. However, some interesting facts have emerged while carrying out experiments of this kind.

In some experiments, cultures, which had been infected with high multiplicities of virus and in which all recognizable growth of the "membrane" type of cell had been destroyed twenty-four hours after infection, continued to produce virus at a gradually decreasing rate until by seventy-two or ninety-six hours after infection they had usually become non-infective. When such cultures, which by then appeared to consist entirely of "polygonal" cells, were reinfected with large seed virus inocula of either the homologous or the heterologous type, they once again produced virus in quantities not significantly different from control cultures infected for the first time, allowance being made for the slightly higher titres obtained in cultures containing growth of the "membrane" type. Fig. 5 shows the result

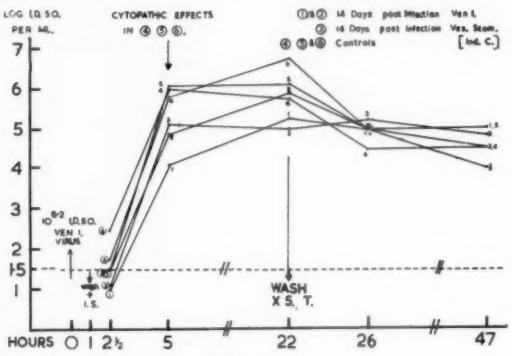


FIG. 5.

of an experiment in which two cultures 1 and 2 had been infected with the Ven. 1 strain (Type 0 foot-and-mouth disease virus) fourteen days previously, and one culture 3 had been infected with the *Indiana C.* strain (vesicular stomatitis virus) fourteen days previously. The cultures were checked for non-infectivity of the media and then they were reinfected with a large inoculum of Ven. 1 strain virus together with three duplicate control cultures not previously infected. After incubation for one hour, the unutilized seed virus was removed by repeated washing including the use of specific immune serum. At six hours the titre of the controls was about tenfold higher than the others, but this was associated with cytopathogenic changes in the "membrane" type cells present in the control cultures. By twenty-four hours, the titres of both groups were very similar and the "membrane" type cell growth had been destroyed in the controls. The cultures were then thoroughly washed, fresh media added and incubated for a further four hours. The two sets of cultures, which were then more or less identical by microscopic examination, gave the same yields of virus by twenty-six hours and by forty-eight hours after infection.

Similar experiments have been made in which cultures shown to have become non-infective, have been reinfected on the seventh day after primary infection and have subsequently produced as much virus as control cultures. Identical results have also been obtained when such cultures have been maintained in growth media containing sufficient colchicine to inhibit mitosis and to prevent the production of new cells after the culture had become non-infective. Thus it would seem that under some circumstances cultures containing the original cell population of "polygonal" type cells can be reinfected as soon as three days after the cultures had become non-infective.

The picture has been made rather more complicated recently, however, by the observation that when a group of duplicate primary cultures are infected with virus and handled in an identical manner with frequent washing and media changing, some of the cultures may become non-infective within seven days or so, whereas others continue to produce virus at a constant low level for more than thirty days.

The factors controlling the loss of infectivity associated with an ability to be reinfected found in some cultures, and the production of chronic infection in others, remain to be identified.

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Clinical Section

President—Sir HENEAGE OGILVIE, K.B.E., D.M., M.Ch., F.R.C.S.

[*May* 10, 1957]

MEETING AT THE ROYAL BERKSHIRE HOSPITAL, READING

Cardiospasm and Epithelioma of Œsophagus Treated by Œsophagectomy.—G. L. BOHN, F.R.C.S.

Mr. F. B., aged 47.

Cardiospasm was diagnosed in 1942. Treatment was by mercury bougie, but this has not been necessary in recent years.

In December 1956 he vomited blood and experienced epigastric pain. There was no increase in his dysphagia and no loss of weight.

Investigations.—Barium meal showed a tumour in the œsophagus, cardiospasm and a duodenal ulcer. Œsophagoscopy revealed a large epitheliomatous ulcer in the mid-œsophagus. Histology: Squamous cell carcinoma.

Treatment.—February 1957: Œsophagectomy with œsophago-gastric anastomosis.

He made a satisfactory recovery but in May 1957 had three epileptiform attacks which are under investigation but are considered to be probably due to cerebral metastases.

October 1957: He remains well. The presence of cerebral metastases has not been confirmed.

In the English and American literature there have been reports of 18 cases of carcinoma arising in association with cardiospasm and this case underlines the points already brought out by previous writers: There is a very long interval between the onset of the cardiospasm and the subsequent epithelioma, usually between fifteen and twenty years. The carcinoma, when it develops, is initially silent and diagnosis therefore tends to be late, so that in only 2 of the cases previously recorded was resection possible. The carcinoma is not infrequently missed on radiological examination and also on œsophagoscopy. A relationship between the two conditions based on chronic irritation sounds feasible but the statistical evidence is somewhat conflicting.

Hypertension Due to Unilateral Renal Lesion.—C. LATTO, F.R.C.S.

Mrs. A. H., aged 38.

History.—2.2.54: For two years has been complaining of headaches, lassitude, breathlessness on exertion, and slight swelling of her ankles in the evenings.

Past history.—Scarlet fever at the age of 13 years followed by probable rheumatic fever (in bed three months). Three normal pregnancies.

Family history.—Father well, aged 75. Mother well, aged 66.

On examination.—Blood pressure 270/150. C.V.S.: Cardiac enlargement, apex beat (thrusting) being palpable in 5th space 5 in. from mid-line. Aortic 2nd sound accentuated. Apical presystolic triple rhythm. Femoral pulses synchronous with radials. Eyes: Grade 3 changes in fundi.

Investigations.—Chest X-ray: Transverse cardiac enlargement and uncoiling of aorta. E.C.G.: Left ventricular hypertrophy and gross strain. Urine: Albumin and pus cells with a few Gram-negative bacilli. Blood urea 35 mg./100 c.c. Maximum clearance test: 44%. I.V.P.: Dye excreted by right kidney which appeared normal. No dye seen on left. Retrograde pyelogram: Urine seen coming from left kidney. X-ray shows small, hydronephrotic left kidney. Ureteric catheter specimen: Right normal; left blood-stained.

Treatment and progress.—As the blood pressure was persistently raised in the region of 270/150 to 240/140 removal of the abnormal left kidney was considered imperative.

Operation (9.3.54).—Left nephrectomy: small atrophied kidney removed.

Pathological report.—"The kidney measures 5 × 3 × 1 cm. The cross section is that of a hydronephrosis in a small kidney."

Post-operative follow-up.—There was an immediate fall in blood pressure to 140/80 with a gradual rise over the next few days and a subsequent fall to the region of 170/90–105. This improvement has now been maintained *for three years* and she has become and remained symptom free.

2.4.57: Blood pressure 170/100. No shortness of breath. No headaches. Eye fields: No hæmorrhage or exudates, residual arterial attenuation.

Discussion.—If we accept the criteria of a successful result laid down at the meeting of

the Section of Urology in 1952 on this subject (*Proceedings*, **45**, 729), that is, a fall in diastolic pressure to 100 mm.Hg or less for at least one year, then this case cannot be included as her diastolic pressure has varied from 90–105 mm.Hg. Nevertheless the fall, from 270/150 to 170/100, has been maintained for three years. This is surely a very successful result.

Langley and Platt (1947) could find only 47 successful cases in the literature and at the Section of Urology discussion in 1952 only 59 cases were recorded as having a good result after nephrectomy.

Apart from the surgical treatment of a phæochromocytoma, a cortical adrenal tumour and coarctation of the aorta, nephrectomy is one of the very rare cures for the disease.

Braasch estimated that 15,000,000 people in the U.S.A. suffer from hypertension and about 30,000 would benefit from nephrectomy. This indicates that we should all keep up the search.

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Dextro-inversio Cordis.—ALASTAIR ANDERSON, F.R.C.P.

E. D., male, aged 19½. A known case of dextrocardia referred for opinion regarding fitness for National Service. He denied any symptoms.

On examination.—Dextrocardia. Apex beat (heaving) palpable in 6th space right anterior axillary line. Insignificant grade 1 basal systolic murmur. Blood pressure 160/80. Femoral pulses synchronous with radials. No situs inversus. Moderate "crater" chest.

Fluoroscopy.—Dextrocardia. Cardiac enlargement. Left aortic arch and descent. No situs inversus.

Cardiogram.—No "mirror image" dextrocardia. Left ventricular hypertrophy and strain pattern in standard and unipolar limbs leads. "Systemic" ventricular leads across chest from V 5 R to V 5 with hypertrophy and "strain" in right chest leads (Fig. 1).

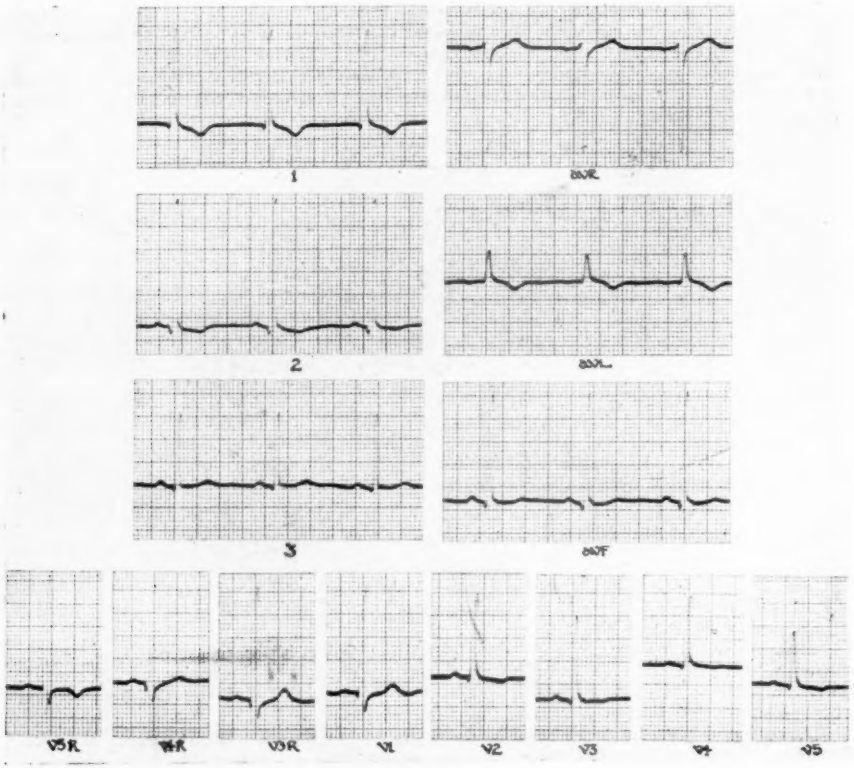


FIG. 1.

Dextrocardia may be classified as: (*a*) Mirror image. (*b*) Dextro-inversio cordis (pivotal). (*c*) Mixed (Fig. 2).

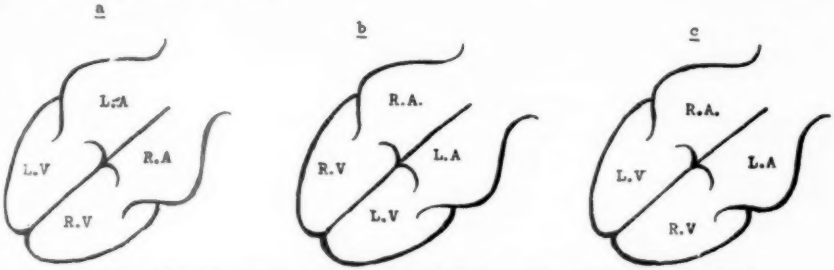


FIG. 2.—After Maurice Lev, M.D., Dept. Pathology, Mount Sinai Hosp., Miami. (1954) *Lab. Invest.*, **3**, 71.

Mirror image.—When "mirror image" dextrocardia is accompanied by situs inversus other congenital cardiac abnormalities do not ordinarily occur. When situs inversus is not present—isolated "mirror image" dextrocardia—other congenital cardiac anomalies are almost invariable and commonly of severe degree.

Dextro-inversio cordis.—Here the position of the chambers is such as would obtain if the heart in lævocardia was simply rotated in a horizontal plane till the apex lies on the right. The morphological left ventricle comes to lie in front and the morphological right ventricle lies behind. This type of dextrocardia is not associated with situs inversus. There is a left aortic arch, and other congenital cardiac defects are almost invariably present and usually gross.

Mixed.—In "mixed" dextrocardia the morphological ventricles are inverted in relation to the atria. Thus the atria lie in a pivotal position, but the morphological ventricles in a "mirror image" position.

I think that this is the state of affairs in this patient: basically pivotal dextrocardia but with inversion of the ventricles so that the anterior and functionally left ventricle is morphologically a right ventricle. This may explain the enlargement of this ventricle. When a morphological right ventricle has to operate against systemic arterial pressure, as for instance in a truncus arteriosus, it enlarges. I suggest it has done so in this case for the same reason.

Multiple Kidney Operations for Cystine Calculi.—G. L. BOHN, F.R.C.S.

Mrs. M. M., aged 39.

1924 (aged 6): Bilateral nephrolithotomy.

1928: Left nephrolithotomy.

1940: Right nephrolithotomy.

1942: Left nephrolithotomy.

In 1951 she was found to have large hydronephroses and multiple calculi in both kidneys. The urine was heavily infected and the blood urea was raised (50 mg./100 c.c.).

The treatment was: (1) To clear both kidneys completely. (This required three more operations, bringing the total to eight.) (2) To eliminate infection with the new antibiotics. (3) To maintain an alkaline urine by means of a vegetarian diet.

Since then the patient has remained well, free of stones and free of urinary infection. Her blood urea was normal in 1956.

Until the 1940 operation, the stones were pure cystine; after that they were a mixture of cystine with calcium phosphate.

Two Cases of Carcinoma of the Ampulla of Vater Treated by Local Excision.—R. G. REID, F.R.C.S.

I.—Mr. F. B., aged 65, was first seen in July 1954 with intermittent jaundice since March 1954. He was deeply jaundiced with urine loaded with bile and the stools clay-coloured. There was a suggestion of a mass in his right hypochondrium. He was obese and appeared unfit for a major operation. Just prior to admission he had a fairly severe melæna for which he was given two pints of blood. The abdomen was explored on August 5, 1954, when the jaundice was found to be due to a small mobile tumour at the ampulla of Vater. The duodenum was incised, the tumour resected locally with diathermy, and the common bile duct re-anastomosed to the duodenum. Section of the tumour showed it to be an adenocarcinoma.

Now, two years and eight months later, he has no symptoms referable to his growth.

II.—Mr. T. P., aged 79, was referred in October 1954 by the skin physician, to whom he had been sent because of four months' intense irritation. He was not very jaundiced, but biliary obstruction was complete and his stools were clay-coloured.

The abdomen was explored on November 8, 1954. The common bile duct and pancreatic duct were both obstructed by a soft mobile tumour of the ampulla of Vater. Although initially, in view of his age and general condition, a short circuit alone was contemplated, after this was done the tumour was again examined and it was seen to be so mobile that a local excision of it was considered worth while, if only to unblock the pancreatic duct. It was, therefore, removed with diathermy. Section showed it to be a well-differentiated carcinoma.

His recovery was interrupted by the development of prostatic obstruction for which he had to have a prostatectomy. He has remained well ever since, and now, two years and six months after the operation, has no symptoms referable to his original complaint.

Discussion.—In showing these cases of tumours of the ampulla of Vater, I wish to stress two things: firstly, the characteristic low malignancy and slow growth of such tumours in which they differ so markedly from carcinoma of the head of the pancreas, and secondly, that surgery carries with it so small an immediate mortality that a local resection may well be worth while if the patient is not fit for a radical operation.

The growth is generally a papillary adenocarcinoma which grows slowly and metastasizes late. It thus differs from carcinoma of the head of the pancreas which with any line of treatment has a poor prognosis. Patients with ampullary growths may live for many years and Morley (1947) records a patient who apparently had a spontaneous cure, for the tumour for which he performed a cholecystenterostomy preparatory to a radical removal was found to have disappeared at the second operation, and a near-by gland which was removed was filled with spheroidal cell carcinoma. The patient lived for another twenty years, dying eventually of a coronary thrombosis.

The first surgical excision of such a tumour was performed by Halstead (1899) in 1898. The approach was through the duodenum and the patient lived for nine months. Many subsequent attempts were made to deal with this condition by limited resections, with a fairly high mortality, until 1935 when Whipple *et al.* (1935) devised a radical two-stage operation. In 1912 admittedly Kausch performed a radical excision anticipating in some respects Whipple's operation, but the operation was considered too severe by most surgeons. The paper by Whipple *et al.* (1935) gave a new impetus to radical operations in this region, and carcinoma limited to the ampulla was treated from then on in this way, if the condition of the patient permitted. The best results are perhaps those of Cattell and Pyrtek (1949) who had one death in 20 resections with a 50% three-year survival. In 1954 Moore and Younghusband (1954) in this country published a series of 8 cases treated by radical excision, one of which died as the result of the operation. At the time of publication it was too early to draw conclusions regarding survival. A study of the specimens obtained shows that the growth was in 50% of cases limited to the ampulla, which suggests that local excision might well have produced a cure.

At this hospital, since 1948, we have had 4 cases of ampullary carcinoma. The first patient, a woman aged 63, died three years and three months after a duodeno-pancreatectomy, from secondary deposits. The other 3, all men, aged 65, 65, and 79 years are alive. They all had a local resection of their tumour two years and nine months, two years and six months, and one year ago, respectively.

The very much better results from surgery for ampullary carcinoma as compared with carcinoma of the head of the pancreas are probably related as much to the early onset of the jaundice, which brings the patient more quickly for treatment, as to the proved lower malignancy of the growth.

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The following cases were also shown:

Myositis Ossificans Progressiva.—Mr. C. M. SQUIRE.

Four Cases Demonstrating Symptoms and Signs of Cardiac Failure in the Newborn Period and Early Infancy.—Dr. J. J. KEMPTON.

Three Cases of Systemic Lupus Hepatitis.—Dr. W. HAUSMANN.

Neurofibromatosis Elephantiasis Nervorum.—Mr. J. JOYCE.

Craniopharyngioma. Symptoms of Temporal Lobe Irritation.—Dr. J. D. KIDD.

Section of Pædiatrics

President—D. V. HUBBLE, M.D., F.R.C.P.

[*April* 26, 1957]

An Outbreak of Infantile Gastro-enteritis (*E. coli O. 128*) in a Small Hospital Maternity Unit

By R. M. MAYON-WHITE, M.D., Ph.D., M.R.C.P., D.C.H.

Introduction.—The outbreak described here occurred in the maternity unit nursery at the West Suffolk General Hospital in the summer of 1955. The main features of the outbreak are indicated by means of an epidemic diagram (Fig. 1) of the type made familiar by Rogers and Keogler (1951).

The outbreak.—The month of June clearly preceded the outbreak. In July there were 2 cases of gastro-enteritis on the children's ward; they appeared to be sporadic cases, neither was particularly ill. In the following eight weeks 14 infants on the maternity ward developed gastro-enteritis, of whom 6 died. 60 other newborn infants at risk escaped infection. On August 16 a meeting of the Control of Infection Committee was called, the help of the Public Health Laboratory Service was obtained for epidemiological bacteriology, and it was decided that all sick infants should be transferred from the maternity unit to the children's ward. A meeting of an enlarged *ad hoc* infection committee was called for the following day.

On August 18 the maternity ward was closed, all mothers and infants were sent home except 2 who were transferred to a private ward temporarily used as an emergency maternity ward; 1 of these infants, and 8 of the 15 infants at risk in the maternity ward on August 18 subsequently developed gastro-enteritis. After cleaning, fumigation and standing empty for two weeks, the maternity unit was reopened on September 1; no recrudescence of gastro-enteritis occurred. In the meantime emergency maternity admissions were diverted to other hospitals in neighbouring towns (15 and 28 miles away).

Bacteriology.—The O. 128 B.12 strain of *E. coli* was obtained from all affected infants born in hospital and from two adult contacts: a maternity ward staff nurse on August 18, and, at a later date, from the children's ward Sister. The organism was not found in the stools of any mothers of affected infants. The same organism was also obtained after discharge from one of the two children's ward cases (Case 1), though not from the other.

Source of infection.—Attempts to trace the primary source were unsuccessful. There is obviously a possibility that infection was conveyed from the children's ward to the infant population of the maternity unit. Supposing that the infection originated either in Case 1 or Case 2, it is possible (*see* Fig. 1) to trace successive waves of new cases separated by an incubation period of seven to ten days. Thus, if Case 2 in the children's ward started the outbreak on about July 15, this infection might have been transmitted by some means to the maternity ward to affect Case 3 about July 24. The third wave is represented by Case 5 in the maternity ward and Case 4 (at home at that time); the fourth wave is a widespread outbreak about August 15–18, when Cases 9, 11, 12, and 13 became ill on the maternity ward, and Cases 6, 7, 10, 14 and 15 became ill in their own homes. In the absence of bacteriological data, this explanation can neither be confirmed nor denied. It is equally possible that Cases 1 and 2 (on the children's ward) had nothing to do with the outbreak in the maternity ward. Case 1 may have acquired the O. 128 strain (which was first demonstrated in his stools three weeks after he had been discharged), by cross infection from Case 3 or Case 5, during the period they were on the children's ward together.

There are other possible origins of the outbreak: the maternity ward staff nurse and the mother of Case 6. The staff nurse may have acquired the organism from the infants in her care. The mother was a maternity ward patient from July 5–19, and July 26 to August 6, her other children suffered intermittent diarrhœa for some weeks at this time: the epidemic strain of *E. coli* was not isolated from their stools or from hers.

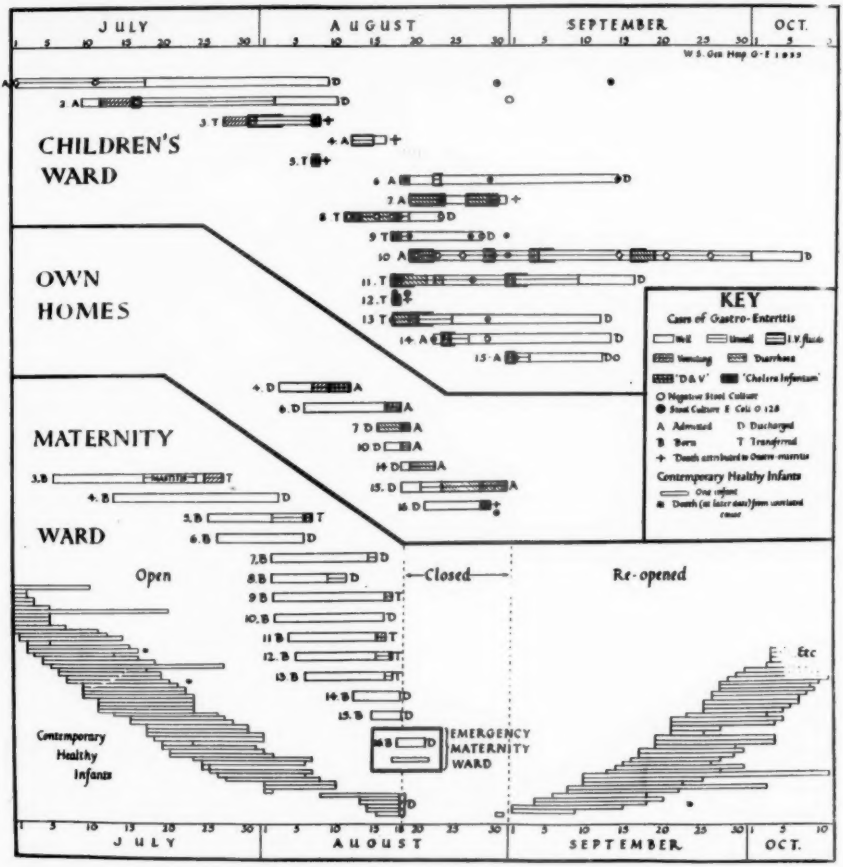


FIG. 1.—This diagram is designed to indicate by time and place the clinical course of each case of gastro-enteritis, to trace the movement of the individual infants, and to give an over-all picture of the development of the outbreak.

Individual cases (indicated by case number) are plotted on a horizontal time scale, the three separate geographical situations in which an infant might be (the maternity ward, his own home, or the children's ward) are indicated; different symbols indicate clinical features.

For example, one may follow Case 4 from birth in the Maternity Unit on July 13, discharged home on August 3; becoming ill at home first with vomiting August 7, then with diarrhœa and vomiting: admitted to children's ward August 12, and dying there four days later.

The contemporary healthy infant population of the maternity ward is also indicated on the same horizontal scale but half the ordinate scale.

Conclusions.—The personal conclusions drawn from this experience may be dogmatically stated as follows: (1) That infantile gastro-enteritis should be a notifiable disease. (2) That for practical purposes the pathogenicity to infants of serologically identifiable strains of *E. coli* should be accepted as a working hypothesis. (3) That the bacteriological investigation of cases of infantile gastro-enteritis should be entrusted to the Public Health Laboratory Service or to bacteriology departments prepared to devote special attention to this work. (4) That professorial pædiatric departments, the pædiatric research units of teaching hospitals, and the specialized gastro-enteritis units of large general hospitals, should regard the prosecution of controlled therapeutic trials in gastro-enteritis as a primary duty. (5) That every general hospital should have a Control of Infection Committee on which the Medical Officer of Health should sit or be represented. (6) That these committees should investigate and report on each hospital outbreak of infantile gastro-enteritis.

Acknowledgments.—This account is based upon the detailed case notes and epidemiological records kept by Drs. M. G. Bridger and I. B. Crawford. I am indebted to Dr. J. Dunscombe for the post-mortem reports and to Dr. R. M. Fry for the bacteriological investigations. I would particularly like to acknowledge the help and support I received from my colleagues on the enlarged Control of Infection Committee.

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Neonatal Œstrogen Excretion and Its Relation to Post-natal Weight Loss

By BRUNO GANS, M.D., M.R.C.P., and J. C. THOMPSON, B.Sc., Ph.D.

Department of Pædiatrics and Group Laboratory, Lewisham Hospital

THIS work represents a preliminary report on œstrogen excretion during the neonatal period and its possible relationship to post-natal weight loss. In this investigation no account has been taken of the other known causes of weight loss, such as the weight of meconium and vernix, the catabolic effects of a difficult labour, or the insensible water losses through skin and lungs.

The hormone estimations were carried out on the twenty-four-hour urine specimens passed, during the first few days of life, by 6 normal male neonates. The urine was collected by means of a Paul's tube strapped to the penis. All 6 infants had an easy birth, and their post-natal course was normal.

The three œstrogens, œstriol, œstrone and œstradiol were estimated by the method of Brown (1955). The 17-hydroxycorticosteroids were also determined, using the method of Appleby *et al.* (1955). The findings were essentially similar in all 6 infants. There were very large (milligram) amounts of œstriol on the first day. The urinary excretion of this substance then dropped rapidly during the next two or three days, and reached values of 1 or 2 μg., similar to those found in adult males, on the fifth or sixth day. Œstrone and œstradiol were found in amounts of 1–2 μg. during the first and second day, and had disappeared by the third day.

The three œstrogens found in the infants' urine showed a pattern similar to that found in their mothers' urine during the twenty-four hours before birth.

The 17-hydroxycorticosteroids showed only slight fluctuations during the first ten to twelve days of life, and their levels appeared to be unrelated to the post-natal weight loss.

Our results show that in all 6 infants the cessation of œstrogen excretion coincides with the cessation of post-natal weight loss. They also show that all 6 infants excreted decreasing amounts of urine until weight loss and œstrogen excretion had ceased, that is, some time between the third and fifth day of life.

The completed data on 4 infants and 2 mothers are shown in Table I.

It is well known that the fœtus and neonate are hydræmic. This hydræmia disappears during the first few days of life. Thorn and Engel (1938) have shown that in experimental animals œstrogen administration leads to salt and water retention. Thorn *et al.* (1938) also found that water retention occurs in women during periods when œstrogen production is high, and that there is a diuresis and a loss in weight after menstruation and post-natally, when the œstrogen level has fallen. Preedy and Aitken (1956) confirmed these findings and found that the weight gain after œstrogen administration was associated with an increase in extracellular fluid and plasma volume. This water and salt retention was attributed by Sophian (1956) to an effect of the œstrogens on the glomerular filtration rate. Thomson (1944) and Woolf and Norman (1957) have shown that the neonate's urine becomes steadily more concentrated during the period of post-natal weight loss.

It appears, therefore, that the infant's urine is of low specific gravity at first, that it becomes more concentrated during the period when the excess water and the œstrogens are being excreted, and that this occurs in spite of the increasing intake of fluid during those first few days of life.

We suggest that some, at any rate, of the hydræmia of the neonate is due to the water-retaining properties of œstrogenic hormones obtained by the infant from its mother before birth. We have shown that these œstrogens are excreted by the infant's kidney during the first few days of life. It would appear logical, therefore, to attribute some of the post-natal weight loss to the water released from the infant's body when the maternal œstrogens have been excreted.

Finally, we would like to suggest a possible reason for the neonate excreting, rather than metabolizing or detoxicating, the œstrogens obtained from its mother. Preedy and Aitken (1956) showed that the water- and salt-retaining properties of œstrogens are particularly

marked in diseases associated with circulatory disturbances of the liver. Emery (1952) found that there is a rapid involution of the left lobe of the liver following birth, and that this involution is due to an alteration of blood flow through that lobe. It seems possible, therefore, that the newborn infant cannot destroy its mother's œstrogens because of the hæmodynamic changes taking place in its liver.

TABLE I.—SHOWING THE WEIGHT LOSS, TWENTY-FOUR-HOUR URINE VOLUME, ŒSTROGEN AND 17-HYDROXYCORTICOSTEROID EXCRETION IN 4 INFANTS, AND THE HORMONE VALUES IN THE URINE OF 2 MOTHERS

Case	Day	Weight (% of birth weight)	Urine volume (ml.)	Œstriol (μg./day)	Œstrone (μg./day)	Œstradiol (μg./day)	17-hydroxy-cortico-steroids (mg./day)
J.	1	100	22	980	0·9	0·3	
	2	96·5	10	600	0·3	nil	
	3	98·5	20	570	0·6	0·1	
	4	98·7	61	20	nil	nil	
	5	98·5	32	5·5	nil	nil	
	6	98·5	35	1·3	nil	nil	
M.	1	100	50	1,446	2·5	0·5	1·39
	2	96·2	45	1,375	1·9	nil	1·42
	3	94·2	14	185	0·06	nil	0·81
	4	92·7	5	11·2	0·06	nil	0·38
	5	95·8	136	6·6	nil	nil	1·77
	6	96·2	197	2·8	nil	nil	1·34
	7	94·2	315	10·1	nil	nil	1·20
	8	97·7	336	3·2	nil	nil	2·15
	9	98·9	235	1·1	nil	nil	0·96
	10	98·9	No specimen				
	11	100·4	285	1·0	nil	nil	1·17
Mother of M.			1,320	15,340	825	41·3	13·5
N.1	1	100	24	694	0·28	nil	1·38
	2	94·0	30	556	0·11	nil	1·76
	3	90·4	25	83·3	nil	nil	1·47
	4	90·0	19	19·7	nil	nil	1·27
	5	91·7	9	4·9	nil	nil	0·57
	6	91·7	34	5·7	nil	nil	1·78
	7	92·6	91	1·4	nil	nil	0·61
	8	94·4	146	2·7	nil	nil	2·02
	9	96·0	136	1·8	nil	nil	1·03
	10	96·4	224	2·2	nil	nil	1·28
	11	98·3	132	0·9	nil	nil	0·48
	12	97·0	100	1·6	nil	nil	1·74
N.2	1	100	40	878	0·6	0·9	0·66
	2	96·2	10	261	0·2	0·1	1·35
	3	93·5	26	359	nil	0·4	1·05
	4	92·5	20	24·3	nil	nil	0·57
	5	95·4	26	4·7	nil	nil	0·73
	6	96·8	94	2·7	nil	nil	0·42
	7	99·1	43	1·1	nil	nil	0·54
	8	101·0	138	3·3	nil	nil	0·65
	9	101·0	142	2·1	nil	nil	0·66
	10	102·5	162	2·4	nil	nil	0·65
	11	103·2	162	2·4	nil	nil	0·52
	12	103·9	98	0·8	nil	nil	0·45
Mother of N.1 and N.2			900	22,400	400	50	27·8

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(*To be continued*)

Section of Dermatology

President—LOUIS FORMAN, M.D., F.R.C.P.

[*March* 21, 1957, contd. from August *Proceedings*, p. 610]

THE following cases were also shown:

Pock Mark Treated by Surgical Abrasion.—Mr. PATRICK CLARKSON.

(1) **Necrobiosis Lipoidica.** (2) **Widespread Purpura for Diagnosis.**—Dr. P. D. SAMMAN.

(1) **Neurofibromatosis and Malignant Pericytoma.** (2) **Liver Disease with Pigmentation and Diabetes Mellitus.**—Dr. OLIVER SCOTT.

Hansen's Disease.—Dr. G. B. MITCHELL-HEGGS, Dr. R. G. COCHRANE and Dr. J. D. EVERALL.

Pigmentation and Leukodermia (Following Dermabrasion).—Dr. G. B. MITCHELL-HEGGS and Dr. J. B. EVERALL.

Reticulosis.—Dr. D. I. WILLIAMS and Dr. R. H. MARTEN.

Multiple Self-healing Epitheliomata (Ferguson-Smith).—Dr. D. E. OAKLEY.

Bowen's Disease.—Dr. J. D. EVERALL. (This case was shown by Dr. G. B. MITCHELL-HEGGS on January 17, 1957, as **Acrodermatitis Continua with Vascular Changes in the Digital Arteries and Venous Channels.**)

[*April* 25, 1957, contd. from October *Proceedings*, p. 774]

Histiocytic Reticulosis.—GEOFFREY HODGSON, M.B.E., M.D.

Male, aged 7 years.

History.—Six months' history of erythematous papular brownish rash. No history of diabetes insipidus.

Clinical findings.—Small firm movable glands axillæ and groins. No splenic or hepatic enlargement.

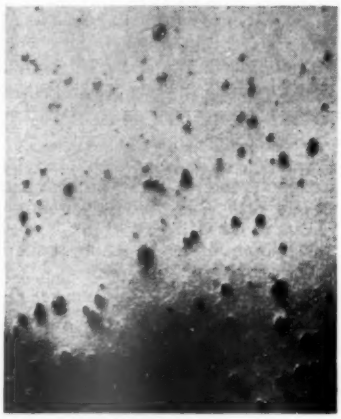


FIG. 1.



FIG. 2.

Multiple non-pruritic flat-topped light brownish pigmented slightly scaling papules 1 mm. to 5 cm. in diameter, in the skin of the face, neck and occipital scalp, back, abdomen, thighs and antecubital fossæ (Figs. 1, 2).



FIG. 3.

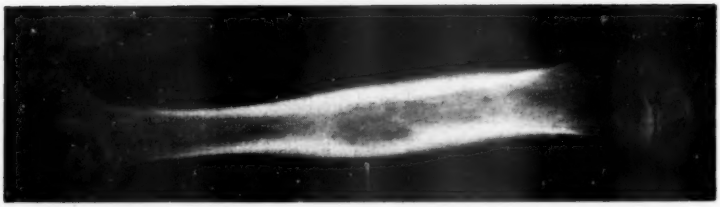


FIG. 4.

Investigations.—X-rays: Areas of bone resorption in skull and right femur (Figs. 3, 4). Chest normal. Abdomen normal.

Blood: Hb 11·8 grams per 100 ml. (80%), W.B.C. 17,600 (polys. 57%, monos. 4%, lymphos. 28%, eosinos. 11%). Packed cell volume 42%. E.S.R. 15 mm. fall in one hour (Wintrobe); corrected by P.C.V. shows doubtful increase.

Liver function tests: Serum total protein 7·0, albumin 3·8 g./100 ml. (Howe). Thymol turbidity 2 units (normal 0–4). Zinc turbidity (Kunkel) 17 units (normal 2–8).

Serum lipoids: 4·6 g./100 ml. Plasma cholesterol 180 mg./100 ml.

Glucose tolerance: Flattened normal curve. *Electrophoretic curve* normal.

Biopsy (Dr. Henry Haber).—There is an area under the epidermis which is heavily infiltrated by two types of cells. One type consists of large mononuclear cells with a vesicular nucleus and abundant cytoplasm of foamy character, and they appear to be forming a syncytial network. The foamy appearance is apparently due to the presence of fat. The second type of cells to be found are those of the eosinophil which are present in either scattered or large groups. The histology is characteristic of Letterer-Siwe disease.

Course.—Slight continued loss of weight. No alteration in X-ray bone appearances or in skin lesions in the last two months.

Three Cases of Parapsoriasis en Plaques.—BRIAN F. RUSSELL, M.D., F.R.C.P.

I.—H. D., male, aged 50. Market porter.

History.—First seen in February 1957 with three years' history of scaly patches on the wrists, arms and trunk, persisting and slowly spreading. General health good.

On examination.—Blotchy erythema of cheeks with scarring of acne. Slightly scaly atrophic greyish-pink areas on trunk in cleavage line pattern. Scaly patches on wrists. Scabbed papules on legs. No lymphadenopathy, splenomegaly or hepatomegaly.

Investigations.—X-ray of chest normal.

Blood: Hb 100%; W.B.C. 10,800; (polys. 69%, eosinos. 2%, lymphos. 25%, monos. 4%). Wassermann reaction negative.

Skin biopsy from left infra-mammary region: Slight acanthosis, focal lymphocytic infiltration in epidermis and moderate lymphocytic infiltration in upper dermis.

II.—E. M., female, aged 43. Housewife.

History.—Following an operation in October 1952 for uterine prolapse, she developed a pelvic abscess which was treated with streptomycin. Shortly after this she noticed a rash on her arms which later spread to the legs. It was not itchy. The lesions slowly extended and did not respond to any treatment. On one occasion only she complained of widespread pruritus. In 1956 she noticed increasing dryness of the skin generally and also of a sore tongue.

Present state.—Pinkish-yellow oval areas with very slight scaling, mostly on the limbs. No lymphadenopathy, splenomegaly or hepatomegaly.

Investigations.—X-ray of chest normal.

8.1.53: Biopsy from skin of arm showed slight non-specific infiltration in upper dermis. Mantoux reaction 1 : 1,000 positive.

Blood: Hb 93%; W.B.C. 9,000 (polys. 59%, lymphos. 37%, monos. 4%).

Treatment.—General ultraviolet irradiation; a course of oral calciferol, and bland local applications have been ineffective.

III.—A. B., male, aged 58. Clerk.

History.—First seen in November 1952 with a twelve months' history of dry scaly non-itchy patches which began on legs and rapidly became widespread. At that time he had plaques of pinkish-yellow slightly scaly skin on arms and legs with atrophic skin on trunk. His general health was good. In spite of treatment the lesions became progressively more extensive until in 1954 the condition resembled ichthyosis.

Investigations.—4.11.52: W.B.C. 8,000 (polys. 72%, eosinos. 1%, lymphos. 21%, monos. 6%). Wassermann reaction negative.

24.11.52: Biopsy of skin from upper arm: Patchy slight hyperkeratosis and parakeratosis, atrophy of epidermis. Slight œdema and non-specific infiltration in upper dermis.

1.7.54: X-ray of chest normal. 23.9.54: Mantoux reaction 1 : 100 negative. 21.11.55: B.C.G. given. 14.2.56: Mantoux reaction 1 : 100 positive.

Treatment.—This has included a course of ultraviolet irradiation, calciferol, mepacrine, vitamin A, thorium-X topically, and bland applications.

Dr. G. B. Dowling: I think that there may be some doubt about the labelling in the first case. For a long while we have, especially at St. John's Hospital, tried to distinguish cases which might develop into a reticulosis, regarding such cases as true parapsoriasis, from those which would never do so, and the distinction is often difficult. The benign cases we suppose to be a kind of very refractory superficial dermatitis.

Dr. Russell: For the diagnosis of parapsoriasis en plaques, I have applied the criterion of non-itchy, slightly scaly, brownish-pink plaques, of long duration, and refractory to all treatment.

Dr. J. T. Ingram: I thought all these cases were parapsoriasis en plaques and the second one I thought illustrated Brocq's leopard-skin pattern of eruption on the trunk. I do not think it is the simple type, but I think it is one of the intermediate types which have been described. I do not think there is any true atrophy, but a semblance of atrophy.

Psoriasis and Mycosis Fungoides.—K. M. HARVEY, M.B. (for BRIAN F. RUSSELL, M.D., F.R.C.P.).

J. S., male, aged 60.

History.—He has had scaly patches on arms, legs and trunk for fifty years. Diagnosed as psoriasis. Eighteen months ago he developed slightly irritable exudative patches on his face and trunk which seemed different from the previous patches. A patch on the abdomen became more irritable and superficial ulceration developed. Throughout this time his general health had been good and there was no loss of weight.

Treatment up till the time of admission to hospital had consisted of local applications only: there had been no superficial X-ray therapy.

Family history.—None of psoriasis.

On examination.—Typical scaly patches of psoriasis on legs, arms and scalp. On the trunk there are numerous infiltrated exudative areas. Two patches on the back show

definite infiltration. A large patch on the anterior abdominal wall shows superficial ulceration. There are a few discrete non-tender lymph glands in axillæ and groins. The liver and spleen are not palpable. There is a right inguinal hernia. Clinical examination otherwise normal.

Investigations.—Biopsy: Right knee: Hyperkeratosis and acanthosis with regular elongation and clubbing of rete pegs, heavily infiltrated with lymphocytes forming Pautrier micro-abscesses.

Left chest: Hyperkeratosis and upper dermal infiltration by lymphocytes.

Right hip region: Parakeratosis, regular acanthosis alternating with atrophy. Moderate infiltration especially of plasma cells and eosinophils in upper dermis.

X-ray of chest normal.

E.S.R.—39 mm. in one hour (Westergren).

Hb 76% W.B.C. 11,200 (polys. 55%, eosinos. 10%, lymphos. 30%, monos. 5%).

Progress and treatment.—Infiltrated lesions on the trunk responded to both X-ray therapy and thorium-X painting. The scaly patches on the legs and arms cleared spontaneously.

Comment.—Clinically this man appears to have had typical patches of psoriasis for fifty years and now also presents with histologically proven mycosis fungoides. It is possible that his long-standing skin eruption was premycotic; alternatively, psoriasis and mycosis fungoides may be presenting together as two separate diseases.

Dr. J. T. Ingram: In Dr. Brian Russell's case it is a retrospective diagnosis. I have never seen psoriasis pass into mycosis fungoides.

Dr. R. T. Brain: I have never seen mycosis fungoides derive from psoriasis, but I have seen typical psoriatic lesions followed by mycosis fungoides. The histology in this case shows that it is not psoriasis.

Mycosis Fungoides Developing on Parapsoriasis en plaques.—BRIAN POTTER, M.D. (for BRIAN F. RUSSELL, M.D., F.R.C.P.).

M. L., female, aged 50.

History.—This patient's eruption has gradually spread over her body since she was 19 years of age. In 1949 at the age of 42 she was seen by Dr. Ian Martin-Scott, and at that time had on the trunk and upper thighs sharply marginated, bluish-pink oval patches. There was no infiltration, the epidermis was questionably atrophic and slightly scaly, and faint brown pigmentation was apparent. There was no regional adenitis. Clinical diagnosis was parapsoriasis en plaques. The eruption has gradually extended since then, no lesions having ever disappeared.

On examination.—The patient, now aged 50, presents on the trunk and extremities a generalized erythemato-squamous eruption in irregular defined lesions, superficial on the extremities and with slight infiltration of the larger areas on the trunk, which latter also show some brown pigmentation (Fig. 1). There is some irritation from these lesions. The clinical impression is now of reticulotic change. There is no lymphadenopathy, and neither liver nor spleen is palpable. Blood count is entirely normal and the chest X-ray is clear.



FIG. 1.—Patchy pigmented erythemato-squamous eruption.

Histopathology.—A biopsy taken in 1949 does not show a specific picture. There is a moderate infiltrate of inflammatory cells in the upper corium, some of which are passing into the epidermis. There are present a number of reticulum cells with somewhat large irregular nuclei.

Biopsy taken recently shows a much more marked infiltrate, containing cells of several different types, nearly all mononuclears, including large numbers of reticulum cells, the nuclei of which show variation in size, shape and content of chromatin. Passing into

the epidermis are some mononuclear cells intermediate in size between reticulum cells and lymphocytes, and in places these are tending to form localized collections within the epidermis (Fig. 2).

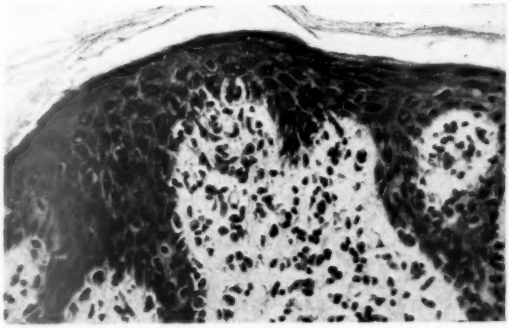


FIG. 2.—Biopsy ×210 taken 9.4.57.

Histologically this is therefore a reticulosis in which the basic cell type is the reticulum cell. Monocytic leukæmia and reticulum cell sarcoma can be excluded in view of the polymorphism of the infiltrate; Hodgkin's disease must be considered, but there is no other evidence of it. In view of the presence of pleomorphic reticulum cells in a polymorphous infiltrate and invasion of the epidermis by atypical mononuclear cells, this case is interpreted as mycosis fungoides (Helwig, 1955).

REFERENCE

HELWIG, E. B. (1955) Mycosis Fungoides. *Proceedings* of the XXth Seminar, *Amer. Soc. Clin. Path., Washington*, p. 93.

Poikilodermia (Jacobi-Lane).—J. S. PEGUM, M.R.C.P.

R. C., male, aged 55.

History.—Fourteen years ago a rash appeared on the left side of the groin. Shortly afterwards a similar rash appeared in the right groin. Since this time the rash has spread gradually over most of the trunk and parts of the legs. The rash irritates occasionally. Parts of it have been treated with X-ray therapy.

In 1956, attended the National Hospital for Nervous Diseases, Queen Square, because he could not keep his balance or walk in a straight line, a diagnosis of disseminated sclerosis was made.

On examination.—Face: Slight redness of right upper eyelid. Both axillæ, the neck, parts of the back, the abdomen, thighs, buttocks, and parts of the legs show diffuse redness, scaling, pigmentation and telangiectasia. B.P.140/90. No pathological enlargement of lymph glands, liver or spleen.

Investigations.—Hb 89%, W.B.C. 10,400 (polys. 62%, eosinos. 3%, lymphos 32%, monos. 3%).

Chest X-ray normal.

Biopsy of skin of abdomen: The horny layer shows hyperkeratosis and in places parakeratosis. The prickle-cell layer is in parts hypertrophic and in parts atrophic. Some of the cells are hydropic. In places there is infiltrate in the epidermis. The upper dermis shows a band-like infiltrate composed mostly of lymphocytes and monocytes. The capillaries are dilated.

Comment.—Clinically and histologically this appears to be poikilodermia (Jacobi-Lane). Unusual is the association with disseminated sclerosis.

Dr. G. B. Dowling: I would describe this as a classical example of poikilodermia of the Jacobi-Lane type. If the patient has disseminated sclerosis this would presumably be an unconnected condition.

Dr. J. T. Ingram: Other cases have been reported of poikilodermia following neurological illness (Katz, F., and Hoogstraten, J. (1946) *Arch. Derm. Syph., Chicago*, **53**, 333).

Poikilodermia Developing Mycosis Fungoides.—E. N. M. JOHNSTON, M.R.C.P.

H. E. E., male, aged 48.

At the age of 17 he began to develop a faint red, non-irritating rash on the neck, trunk, thighs and arms, especially affecting the flexures.

He was shown to the Section in 1936 by Dr. G. B. Mitchell-Heggs and Dr. F. W. Jacobsohn as a case of poikilodermia of Jacobi with polydactyly (*Proceedings*, **29**, 717). At that time the lesions were described as follows: "On the sides of the neck there are reddish-brown pigmented and erythematous spots, slightly depressed and surmounted by a scale within intervening white skin, atrophic in some parts. The appearance resembles reticular marbling seen in ephelis ab igne. Faintly brown erythemato-squamous lesions were present on the trunk."

The histology was reported as showing: "Upper third dermis. Dense infiltrate of round cells in an œdematous reticulum. Histocytes and chromatophores were also present. The infiltrate extended into the papillary body and had a moderately sharp lower border."

In 1936 he was treated with thorium-X with some improvement but this was not maintained.

He was first seen at St. Thomas' Hospital in 1951 and was shown to the Section by Dr. Waddington in February 1951 as a case of poikilodermia-mycosis fungoides. At that time he complained that six months previously the lesions had started to itch intensely (twenty-four years after the onset of the eruption). The areas of poikilodermia were unchanged but, in addition, there were now bluish red scaly infiltrated plaques on the left side of the chest and abdomen and bilateral inguinal adenopathy. There were no other abnormal clinical findings. A chest X-ray and several blood counts were all normal.

The histology of two biopsy specimens was reported on as follows (*Proceedings*, **44**, 675):

From infiltrated plaque: "Severe irregular epithelial hyperplasia and infiltration of the upper layer of the dermis by inflammatory cells of almost all types. The infiltrate freely invades the epidermis and extends downwards into the dermis along the line of vessels and appendages. The appearances are very suggestive of mycosis fungoides."

From area of poikilodermia: "Epithelial depigmentation and slight hyperplasia and superficial dermal and epidermal infiltration by inflammatory cells. There is also some superficial vascular dilatation and elastic tissue has disappeared from the upper third of the dermis. The appearances are compatible with the diagnosis of a premycotic eruption."

A considerable amount of radiotherapy to the more infiltrated lesions has been given with great benefit. However, further plaques have continued to appear, some infiltrated and some being little more than erythema and scaling and these have gradually increased in number until the present time.

Since 1955 raised nodules and ulcerated lesions have appeared from time to time, some showing a marked horseshoe configuration. These have been treated with superficial X-rays with very good effect. The itching is still extremely troublesome.

Mycosis Fungoides Treated with Prednisone.—L. FORMAN, M.D., F.R.C.P.

W. P., male, aged 57.

History.—Commenced 1952. Erythematous plaques, "parapsoriasis", over the trunk, not scaling, not irritable, not infiltrated. Became widespread and patterned enclosing normal areas of skin. Subsequently irritation and oozing in some of the plaques.

Section, taken 1952, at this stage was not sufficiently definite to diagnose mycosis fungoides.

Treatment (1952–53).—Thorium-X 1,000 e.s.u. per c.c. of spirit was applied to the areas resembling parapsoriasis en plaques. The treated areas involuted, but relapsed towards the end of 1953, and became almost confluent; the itching more severe, and the section more typical of the erythrodermia of mycosis fungoides.

1954: X-ray treatment was given and the eruption faded. The whole body surface was irradiated in courses until the beginning of 1956.

October 1956: There was generalized itching and relapse of the erythrodermia. Prednisone 30 mg. a day produced a prompt remission of the erythema and scaling, and of the itching, and continued from November 1956 to January 1957 when the dose had been diminished to 15 mg. a day. The eruption relapsed and small nodules have appeared on the shoulders during the past six weeks. The prednisone was again increased to 30 mg. a day and the severity of the dermatitis and itching diminished. However, no effect has been produced on the nodules.

Investigations.—W.B.C. 6,600; normal differential without eosinophilia.

November 1956: Bone-marrow showed increased plasma cells, eosinophils, megakaryocytes and granulocytes showed left shift. This finding is common in mycosis fungoides and similar conditions (Dr. R. L. Waterfield).

November 1956: Total protein 7·9, albumin 3·3, globulin 4·6 g.% (moderately increased).

November 1956: X-ray showed small areas of calcification within the brain and throughout the lung; soft tissue of the thigh no evidence of calcification—probably old miliary tuberculosis.

To-day, a typical patterned erythrodermia with nodules of mycosis fungoides is to be seen.

Section of Ophthalmology

President—R. C. DAVENPORT, F.R.C.S.

[*May* 9, 1957]

Arteriosclerotic Optic Atrophy

By DONALD J. LYLE, M.D.
(*Cincinnati*)

INTRODUCTION

WITH the lengthening of the human span of life and the increase of the aged population there is a change in the character and importance of disease. With the control or abolition of infections and a variety of heretofore undiagnosed maladies, which used to terminate life at an earlier age, the insidious diseases of senescence are coming to the fore. One of these is arteriosclerosis. As ophthalmologists we are interested in the sub-class, atherosclerosis, which may very well become the medical public enemy number one.

Atherosclerosis is not a generalized process but is manifested by local atheromatous lesions. There may be some dissemination but the distribution is confined to certain areas where there are curves and branching of blood vessels, as at the knee of the internal carotid artery, and where the vessels are restricted or fixed, as in the optic foramen. In these places the uniform flow of the blood stream is disturbed and eddies occur. These are favoured sites for both atherosclerosis and thrombosis.

Arteriosclerotic, or to be more exact atherosclerotic, optic atrophy is a definite entity. It should replace various terms such as pseudo-glaucoma, soft- and low-tension glaucoma. It is included in the so-called cavernous type of optic atrophy.

Symptomatology.—The individual with arteriosclerotic optic atrophy is past middle life. There is usually evidence of arteriosclerosis elsewhere in the body. The retinal vessels may show involvement, the mentality may be affected and other cerebral changes may be noted. However, the chief complaint is of visual loss.

Ophthalmoscopic examination reveals optic atrophy of so-called primary type with pallor of the disc and cupping resulting from axon degeneration without gliosis or fibrosis at the papilla. The cup margin frequently shows depression and degeneration, the result of sclerosis of cilio-retinal vessels (a better term might be cilio-papillary vessels) from the circle of Zinn (Haller) giving the disc rim the appearance of atrophic shelving (Fig. 1).

This depressed flange surrounding the deeper cupping is of importance in diagnosis as it indicates sclerosis of cilio-retinal vessels as well as the probable involvement of the vessels up-stream, the ophthalmic and carotid arteries and their branches, which supply the optic nerves and chiasm. This sclerotic rim must be differentiated from the scleral crescent of developmental origin, of no clinical significance, and from other circumpapillary degenerative conditions.

In this discussion we are not interested in the other types of arteriosclerosis although hyperplastic arteriosclerosis or arteriolosclerosis may influence the production of atheromatous changes. Obliterative arteriosclerosis more closely resembles atheromatous arteriosclerosis as the intima is chiefly involved in both conditions. However, the obliterative type does not have the degenerative changes as seen in atheromas. Obliterative arteriosclerosis may be seen in the larger vessels at the papilla.

Pathology.—Post-mortem examination of the areas of involvement shows sclerosis of larger vessels with hypertrophy of the subendothelial layer between the internal and elastic lamellæ, diffusely localized or in patchy plaque formation. The elastic tissue is disorganized and atheroma develops with lipid, hyaline and calcium deposits. Neovascularization may give rise to hæmorrhages within the atheroma. These lesions may be seen in the vessels at the papilla extending to the second bifurcation. The smaller vessels, including the cilio-retinal arteries, show proliferative endarteritis.

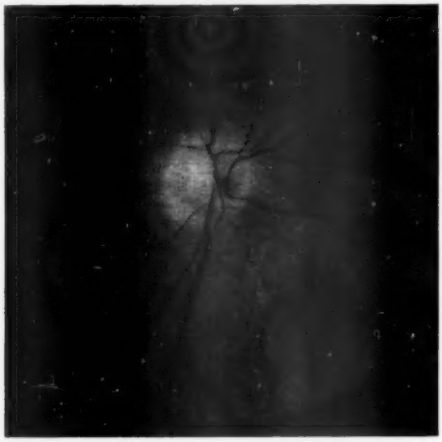


FIG. 1.—Atherosclerosis with atrophic cupping of papilla, with atrophic rim.

The chiasm and optic nerves appear to become first affected in the vicinity of the involved blood vessels, the degeneration gradually extending in both directions, in a type of cavernous optic atrophy (Schnabel's caverns).

The cupping of the optic papilla is probably the result of:

1. Atrophy and shrinking of axons.
2. Compensatory and pathologic (sclerotic) attenuation of blood vessels.
3. Recession of weakened lamina from the normal intraocular pressure.

Vascular anatomy.—Visual acuity and visual field loss in arteriosclerotic optic atrophy is produced by denied nourishment and/or destructive pressure on the optic nerves and chiasm. Occasionally the optic tract may be involved with delayed ophthalmoscopic evidence of optic atrophy.

I. Denied nourishment through arteriosclerosis may affect:

A. The optic chiasm and intracranial optic nerves which are supplied by the anterior portion of the circle of Willis, including the anterior cerebrals, anterior communicating and internal carotids. The posterior cerebrals, middle cerebrals and anterior choroidal vessels supply the posterior chiasm and optic tracts.

B. The intra-canalicular and intra-orbital portions of the optic nerves are supplied by the ophthalmic artery and its branches, chief of which are:

(1) Retinal artery of questionable blood supply to the papilla excepting through small interstitial branches which anastomose with the cilio-retinal vessels.

(2) Numerous branches which invade the optic nerve through the septal system to supply the periphery of the nerve.

(3) Recurrent central artery, a branch of either the central retinal artery or a separate vessel from the ophthalmic which supplies the axial portion of the optic nerve.

(4) Short posterior ciliary arteries to the circle of Zinn (Haller) and thence as the cilio-retinal vessels (cilio-papillary) to supply the optic papilla and surrounding area.

It might be mentioned here that the ophthalmic artery does not usually supply the intracranial portion of the optic nerve but runs subdurally and gives off no branches until it reaches the optic canal and orbit where it supplies the optic nerve. However, a normal intradural variation of the ophthalmic artery might supply the intracranial portion of the optic nerves.

I should like to mention some experiments Dr. Hunter and I performed in investigation of the blood supply to this area. This work was instigated by the occurrence on occasions, fortunately infrequent, when vision was irreparably lost following trapping operation for aneurysm in the chiasmal area. It was decided to determine the blood supply to this area. Both animal (*macacus rhesus*) and human material were used.

Yellow latex was injected through the carotid and basilar arteries into the cerebral vascular tree, after exsanguination and saline wash, with brain in situ. The vascular pattern was studied under the dissecting microscope. The procedure was more difficult in the case of human material because, during the short time elapsing between death and injection, post-mortem changes occurred which interfered with complete vascular filling.

From this study we determined that there was a rich supply or network of small nutrient arteries to the optic chiasm and intracranial optic nerves from the vessels mentioned above. We concluded that the neurosurgeon, inadvertently or of necessity, stripped away these fine vessels, thus interfering with proper blood supply to the intracranial nerves and chiasm even though there was adequate collateral circulation. Extreme caution on the part of the neurosurgeon must be exercised to prevent this occurrence.

II. Destructive pressure upon the axons may occur in:

A. The chiasmal area from the large vessels which normally are in contact with the chiasm and terminating optic nerve (Fig. 2).



FIG. 2.—Atrophy of axons in the optic chiasm caused by pressure and probably denied blood supply from sclerotic arteries.

B. Within the narrow confines of the optic foramen where the ophthalmic artery is in contact with the optic nerve.

At post-mortem examination an almost constant observation is the grooving of the chiasm by the knee of the internal carotid arteries. Although there is no grooving of the optic nerve by the ophthalmic artery in the optic foramen they are in contact in a constricted space which does not allow for expansion. Even in the retina atheromatous changes displace the structures.

DIFFERENTIAL DIAGNOSIS

Differentiation of arteriosclerotic optic atrophy from other conditions having similar symptoms may be determined by history and examination. Roentgenological observation is of great importance, particularly skull films of the sellar area. In arteriosclerosis frequently calcium deposits are seen in the knee of the carotid artery and its vicinity. (Tumours may produce evidence of their presence by destruction or hyperplastic or other changes in the bony contour.) Arteriograms are of great importance. Occasionally ventriculograms and encephalograms may show cerebral degeneration, ventricular and external changes. Measurement of retinal arterial pressure, as described by Bailliart forty years ago, is now being applied as an aid in determining the patency of the ophthalmic and carotid arteries. Further investigation may prove this test to be of great value in diagnosing arteriosclerosis as well as other conditions obstructing circulation and affecting the visual system.

The destruction of the axons in arteriosclerotic optic artery, by either pressure or denied blood supply, produces visual field loss which may be of some diagnostic importance if the lesion occurs in the carotid-chiasm area (Fig. 3). In this location nasal, binasal and altitudinal field loss, depending on the position of the vessels, may occur. This must be

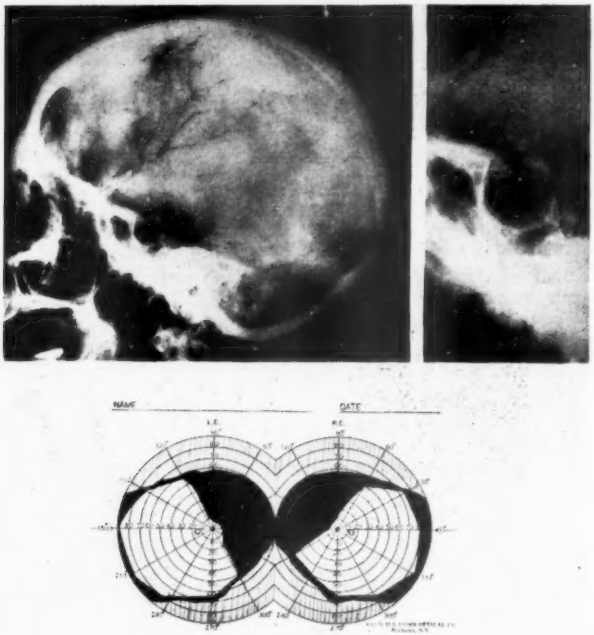


FIG. 3.—Calcium deposits seen in the knee of the internal carotid arteries which have produced binasal field loss.

differentiated from the field loss produced by other lesions most frequently producing optic atrophy. They are:

A. In the chiasmal area:
- (1) Adenoma of the hypophyseal gland.
- (2) Craniopharyngioma.
- (3) Meningioma of the tuberculum sellæ.
- (4) Internal hydrocephalus with dilatation of the optic recess.
- (5) Aneurysm in adjacent vessels.

There is a possibility that traction and pressure from opticochiasmatic arachnoiditis might cause mechanical as well as inflammatory damage to the nerve. The most characteristic field loss of hypophyseal adenoma in earlier stages is temporal or bitemporal; with craniopharyngioma there is no characteristic field loss; nor is there in aneurysm. Meningioma of the tuberculum sellæ may produce an altitudinal and temporal loss; internal hydrocephalus a bitemporal loss.

B. In the optic foramen:

(1) Constriction of the bony foramen in osteitis deformans or Paget's disease, leontiasis ossea and hyperostosis frontalis interna may produce optic atrophy but the usual cause is from vascular involvement producing chorioretinal degeneration. Other types of bony constriction are found in the young, such as osteopetrosis (Albers-Schönberg disease) but are of no significance as they are hereditary congenital developmental anomalies.

(2) Dilatation of the bony foramen with compression of its contents by invading neoplasms may occur most frequently from meningioma in the aged individual. Dilatation frequently occurring from astrocytoma (glioma) of the optic nerve, neurofibroma and retinoblastoma are in a younger age group and are therefore not significant.

Atherosclerotic involvement within the optic foramen and along the course of the optic nerve usually produces sector field loss which is not characteristic. Arteriosclerosis of the recurrent central vessel may produce central field loss which requires differentiation from

cerebro-macular degeneration from other causes, and from toxic and inflammatory conditions.

It is quite possible, and most probable, that mechanical pressure from these various conditions may be exerted, not only upon the optic nerves and chiasm, but also upon the vessels nourishing these axons and thus interfere with an adequate blood supply, with resultant atrophy.

Determination of the intra-ocular tension is of importance as there is a similarity between arteriosclerotic optic atrophy and glaucoma in the appearance of the atrophic and cupped papilla. In order to eliminate the possibility of intermittent periods of ocular hypertension not present at the time of examination, facility of outflow should be determined and the angle examined with the gonioscope. It does not seem reasonable to assume visual damage with optic atrophy has occurred in individuals with normal intra-ocular pressure.

Vascular occlusion of the ophthalmic artery and/or internal carotid artery from thrombosis must be considered. This condition is usually unilateral and in a younger age group than the arteriosclerotic, although atheromatous changes may induce the formation of thrombus. A relatively frequent location for thrombus is in the internal carotid artery above the bifurcation of the external carotid, up to and including, the ophthalmic artery. The symptoms vary according to age, extent of obstruction and location. If the collateral circulation through the circle of Willis and orbit is interfered with the condition is quite grave. As the internal carotid supplies the frontal, temporal and parietal lobes one may expect homonymous hemianopia or quadrantanopia. If the ophthalmic artery is obstructed complete ipsilateral blindness occurs unless there is adequate collateral circulation. In addition, hemiparesis and hemianæsthesia, headache, aphasia and other mental disturbances may be present. In this condition angiography is the most valuable aid to diagnosis. Ophthalmodynamometry may prove a significant adjunct.

Differentiation should be made from so-called temporal arteritis, a disease which should also include other arteries in various parts of the body. The ophthalmic artery and its branches are frequently affected. This condition occurs in elderly people with arteriosclerosis.

In arteritis there is cellular infiltration of the vessel walls with various stages of inflammation, frequently terminating in granulation and necrosis. Temporal and orbital swelling and tenderness are prominent features. In arteriosclerosis alone the degenerative process is less acute and the progress less rapid, without pain or fever, and with less marked symptoms of generalized vascular involvement.

Visual field loss in temporal arteritis is not characteristic. It may resemble any of the types found in arteriosclerosis. Ophthalmoscopic examination may reveal more activity in the fundus in arteritis, with hæmorrhages and exudates in addition to vascular inflammation, and sclerosis with degeneration and atrophy. Phlebitis, and venous and arterial occlusion of the retinal vessels occur with relative frequency.

Treatment

As the ætiology of atherosclerosis is not conclusively established treatment is far from satisfactory. It is believed that these atheromatous changes are the product of disturbed systemic lipid metabolism in which hypercholesterolæmia is a prominent feature.

Treatment must be directed toward prevention. Normal adjustment of blood lipids should be attempted. Control of systemic diseases such as hypertension, nephritis and diabetes is imperative. When diagnosed, anticoagulants are advocated (heparin and dicoumarol), vasodilators are used. Antibiotics may have a place if infection is suspected.

Prognosis depends, for a great part, on the adequacy of the collateral circulation to the circle of Willis and external carotid anastomoses.

Diagnosis of Arteriosclerosis

Diagnosis of arteriosclerotic optic atrophy can be supported by the following observations:

(1) The condition is found in elderly persons.

(2) Arteriosclerosis is present which may be suggested by the appearance of the retinal or choroidal vessels. Symptoms produced by arteriosclerosis elsewhere in the body may support the diagnosis.

(3) The optic papillæ are pale and cupped and may be rimmed with a shelf of atrophy.

(4) The most typical visual field losses are nasal or altitudinal from involvement in the chiasmal area. Peripheral segmental loss, rarely concentric constriction or central scotoma, may be found with involvement of the optic nerves. These field losses are not characteristic and not necessarily of diagnostic value.

(5) Intra-ocular tension is normal.

(6) Radiological studies reveal shadows in the knee of the internal carotid arteries in the sellar area. Arteriograms may reveal sclerosis of vessels supplying chiasm and optic nerves. Ophthalmodynamometry may determine reduced blood supply from vascular occlusion.

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Section of Endocrinology

President—T. RUSSELL FRASER, M.D., F.R.C.P., D.P.M.

[*May* 22, 1957]

DISCUSSION ON HASHIMOTO'S DISEASE

Dr. R. W. Luxton (Crumpsall Hospital, and the Christie Hospital and Holt Radium Institute, Manchester):

The Clinical Aspect

Forty-five years ago, Hashimoto (1912) described the clinical, pathological and histological features of 4 patients with a goitre, and named the condition Struma Lymphomatosa. In his summary of their clinical aspect, he states that the patients were over 40, in good general health and showed no visceral disease. The goitre was discovered incidentally in all cases, had developed gradually and was freely movable, but was firm enough to suggest malignancy. It produced no severe pressure symptoms and there was no lymphadenopathy.

My task is to review the clinical picture of Hashimoto's disease as it is seen to-day. It has been described as rare, but it is much commoner than the general physician is apt to believe. It is worth consideration in any patient with a goitre and in any patient with hypothyroidism, and is the probable diagnosis when hypothyroidism is associated with a goitre in middle age, if goitrogens are excluded. Although most often seen in the fourth, fifth and sixth decades, cases arise from the 8th to the 80th year. Women predominate; of the 41 patients of my own series only 3 were men.

Clinically, the typical patient has hypothyroidism and a firm goitre, and is well illustrated in a woman aged 41, who had gained 3 st. in weight in three years, was constantly cold and mentally abnormal (Fig. 1). For one year she had had a goitre which was diffuse, firm and lobulated. Her serum cholesterol was 525 mg./100 ml. and her serum flocculation tests were abnormal.

The Goitre

The goitre is usually *recent*—having existed a matter of twelve months or so. Some patients have had a goitre for several years, however—in my series, for five, eight, nine, thirty and thirty-one years. The goitre is usually diffuse, and of small or medium size although it can be large. Clinically, it may seem to involve one lobe only, but histologically the whole thyroid is commonly affected. The texture of the goitre is characteristically firm and the surface smooth and lobulated. The gland is not fixed. As in Hashimoto's original cases, the goitre is often an incidental observation. Some patients have mild pressure symptoms (17 in my series)—a feeling of constriction in the neck and sometimes dysphagia. Hoarseness of the voice is not uncommon. Very occasionally there is pain and tenderness (noted in 2 of my patients).

There are two important variants of the clinical syndrome as regards the goitre: (1) it may be relatively soft, or soft with firmer areas, and (2) the goitre may be absent.

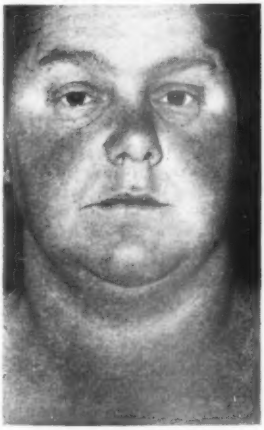


FIG. 1.



FIG. 2.

FIG. 1.—Typical Hashimoto's disease, showing myxœdema and diffuse goitre.

FIG. 2 is a photograph of a woman aged 36 who showed clinical myxœdema. She was constantly cold, with puffy face and hands, a sluggish bowel and a sluggish mind. Her serum cholesterol was 490 mg. per 100 ml. and her radio-iodine uptake was at myxœdema level. The serum flocculation tests were negative. In the absence of a goitre and with negative flocculation tests, primary myxœdema was diagnosed. However, the thyroid isthmus was palpable, not because it was enlarged but because it was firm. The serum precipitin test was strongly positive. Finally, biopsy of the thyroid gland showed histology typical of Hashimoto's disease.

After subtotal thyroidectomy, it is unusual for a goitre to reappear, but this happened in one of my patients two years after operation. When a hemithyroidectomy is done, the remaining lobe not uncommonly enlarges and may cause pressure symptoms, as in 2 of my patients. In one such case, the goitre recurred seven years after operation. Recurrence of goitre may follow cessation of treatment with dried thyroid gland. The regional lymph nodes are not often enlarged *clinically*.

Hypothyroidism

Gross symptoms of myxœdema may be present when the patient first attends, but often the patient's only complaints are the minor symptoms of hypothyroidism—gaining weight, feeling cold and general slowing down of physical and mental processes. "Rheumatic" pains are common in muscles and joints. I am impressed with the frequency not only of osteoarthritis but also of rheumatoid arthritis in this disease. Mental changes were present in 5 of my patients. Great apprehensiveness is a feature and leads to a refusal of investigation or photography until after they have regained their morale and good looks by treatment with dried thyroid gland.

Hashimoto made no reference to hypothyroidism in his patients until after operation. Although the natural course of the disease leads to hypothyroidism, a small proportion of patients have hyperthyroid signs and symptoms at the onset, and a larger proportion are euthyroid when first seen. Of 16 pre-operative patients 9 were hypothyroid, 5 euthyroid and 2 hyperthyroid. It would appear that although many thyroid follicles may be damaged, the remainder can compensate for long periods.

Hyperthyroidism

Hyperthyroidism is well recognized as an early phase. Typical symptoms and signs, including eye signs, have been described, and the B.M.R. recorded up to +69%.



FIG. 3.

FIG. 3, taken in 1951, shows a woman then aged 42. As hyperthyroid symptoms she had lost 1 st. in weight in four months and showed sweating, tremor and upper lid lag. The B.M.R. was +38%. She had noticed a goitre for one month, it was diffuse and moderately firm. The spleen was palpable. Serum flocculation tests were abnormal. A diagnosis of Graves' disease was made and methyl thiouracil given in average dosage for four months, when she showed hypothyroidism and a larger and harder goitre. A thyroid biopsy showed advanced Hashimoto's disease. Despite the hyperthyroid onset, after five years' treatment with thyroid grains 3 daily, this patient is now euthyroid and the goitre has disappeared.

Euthyroidism is commoner than hyperthyroidism when the patient is first seen.

A woman aged 36 was admitted to hospital for abdominal pain which led to a laparotomy. A goitre was an incidental observation. The serum flocculation tests were abnormal. She was clinically euthyroid and the serum cholesterol was 188 mg. per 100 ml. Histologically, the thyroid showed Hashimoto's disease.

Visceral Involvement

Hashimoto recorded that his cases showed no visceral involvement. I believe that visceral disturbance may arise in this disease.

Liver.—In 1947 a woman with myxœdema showed a diffuse goitre and hepatomegaly. The spleen was not then palpable. Two years later, after radiotherapy to the goitre, and thyroid grains 2 daily, she was euthyroid and without a goitre. Later, the spleen became palpable. In 1955 laparotomy revealed a grossly cirrhotic liver and splenomegaly but the portal venous pressure was normal. To-day this patient is jaundiced, hypercholesterolæmic, with liver palms, spider nævi and ascites. The hepatic histology was very unusual (Dr. James Davson): "The picture was that of rather advanced diffuse hepatic cirrhosis.

Normal lobules were barely recognizable. The liver cells formed compact nodules of different sizes, apparently due to regeneration hyperplasia. The nodules were separated by bands of cellular vascular connective tissue, often wide, the infiltrating cells being mainly plasma cells and lymphocytes. An unusual feature was the absence of proliferating bile-ducts. The histogenesis of this cirrhosis was not clear. Cholangio-hepatitis and cirrhosis developing in a fatty liver were unlikely causes. Post-hepatitis cirrhosis was a possibility. There was no evidence of sarcoidosis, brucellosis, or hæmochromatosis."

It is worthy of note that plasma cells, connective tissue, lymphocytes and aggregates of lymphocytes are present—reminiscent of the histological changes in the thyroid gland in Hashimoto's disease. I am tempted to describe it as "Hashimotosis of the liver"! Of course, one cirrhosis does not establish a complication any more than one swallow establishes a summer, but each makes one look for others.

In 1952, the above case, and others with palpable spleens, led to a study of liver function tests in Hashimoto's disease, especially of plasma proteins by qualitative methods. At about the same time, Dr. R. T. Cooke, Pathologist at West Hartlepool, also observed, independently, that the serum flocculation tests may be abnormal in Hashimoto's disease. The figures I shall quote are from my own patients, but the general conclusions about the tests were reached jointly with Dr. Cooke, when he and I made an analysis of our combined cases (Luxton and Cooke, 1956).

Table I shows results of serum flocculation tests in 39 cases of Hashimoto's disease in relation to treatment. The diagnosis was confirmed histologically in 34 cases. Previous treatment by surgery, X-radiation or dried thyroid affects the results of the tests:

TABLE I.—SERUM FLOCCULATION TESTS IN 39 CASES

Untreated	16
Tests abnormal	14
Surgery ± X-radiation	5
Tests abnormal	3
Surgery ± X-radiation and thyroid	18
Tests abnormal	1

Dr. Cooke and I concluded:

(1) In untreated patients, the serum flocculation tests are positive sufficiently often to make them of diagnostic value.

(2) In the *typical* case, the best treatment is thyroid by mouth, as indicated by Crile (1954). Thus treated, hypothyroidism disappears, the goitre lessens considerably in size, and plasma proteins and flocculation tests return to normal. Many months—up to two and a half years—may elapse before the reversion occurs.

(3) The colloidal gold test is a little more sensitive than the thymol turbidity, but not always, and both tests are necessary.

Spleen.—The spleen was persistently palpable in 6 of my first 24 patients, but in only 1 of the next 17 patients.

Kidney.—In myxœdema, a moderate trace of albuminuria, peripheral pitting œdema and hypertension occur quite commonly as separate manifestations, without implying renal disease. On that account, when these 3 clinical findings *coincide* in an individual with hypothyroidism, the diagnosis of underlying chronic renal disease may be rejected prematurely.

Repeated examination for albuminuria was made in 37 patients with Hashimoto's disease. 15 showed an occasional trace of protein; 6 further cases showed persistent albuminuria. 4 of the 37 patients had evidence of a nephropathy. I present these cases with some reserve as I could not investigate them fully but hope to have opportunity for further study.

In 2 cases a nephrotic syndrome occurred and some details thereof are given in Table II.

TABLE II

Pitting œdema	Urine albumin (grams/litre)	Total serum protein (grams/100 ml.)	Serum cholesterol (mg./100 ml.)	Blood pressure	Comment
++	3	5	776	130/80	Casts +
++	12	4·3	880	150/85 rising in ten months to 240/115	Urea clearance 15%

Features common to the two patients are—both were aged 54 years, both had changes of rheumatoid arthritis in the hands, both were hypothyroid and in neither case did the renal symptoms improve when dried thyroid was given, the serum protein showed decreased albumin and increased α_2-globulin. Amyloid disease is a possibility but further evidence is needed.

Two other patients with nephropathy had persistent albuminuria and hypertension bu. no œdema or increase in blood urea (Table III).

TABLE III

Age	Albuminuria	Blood pressure	Comment
58	Persistent	190/110	I.V.P. normal
65	Persistent	225/125	Euthyroid

So far as I can discover, nephropathy in Hashimoto's disease is hitherto not recorded.

Association of Hashimoto's Disease with Paget's Disease of Bone

The patient previously described with hyperthyroidism and Hashimoto's disease developed pain in the back in 1952 and routine X-ray of the pelvis revealed Paget's disease in the left ilium and ischium, naturally regarded as incidental. Three years later two clinical cases of Paget's disease combined with Hashimoto's disease were seen:



FIG. 4.

E. H., female, aged 42. Goitre for three months (Fig. 4). Clinically euthyroid. Serum flocculation tests positive. Right tibia, bowed, thickened, warm (Fig. 5). Radiology of tibia: characteristic of Paget's disease. Surgical biopsy of thyroid: definite but early Hashimoto's disease.



FIG. 5.

A. Y., female, aged 48. Goitre for three months. Clinically hypothyroid. B.M.R. −15%. Serum flocculation tests positive. Surgical biopsy of goitre: struma lymphomatosa. Left tibia was thickened, bowed, tender. Changes, clinical and radiological, were present in a metacarpal. X-ray appearances had suggested polyostotic fibrous dysplasia in left tibia, one metacarpal and right great trochanter. A bone biopsy of left tibia showed cement lines and mosaic pattern typical of Paget's disease.

During 1956 a limited radiological bone survey was made in 35 patients with Hashimoto's disease by my colleagues Dr. J. Blair Hartley, Dr. J. B. Fawcitt and Dr. J. Cowen. In all, 7 of the 35 patients showed radiological bone changes of Paget's disease. Statistical analysis shows that the prevalence rate of Paget's disease in this series of patients with struma lymphomatosa is highly significant (Luxton, 1957). If confirmed, it may offer a clue to the pathogenesis of Paget's disease of bone.

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Dr. Deborah Doniach, Mr. R. Vaughan Hudson and Dr. I. M. Roitt (Middlesex Hospital and Courtauld Institute of Biochemistry):

Diagnostic Aspects of Lymphadenoid Goitre

In classical cases of Hashimoto's disease which present with advanced myxœdema and a large, firm, symmetrical goitre, a presumptive diagnosis can be made on the clinical findings. In practice such cases must be rare since it is estimated in the literature that only 20% of lymphadenoid goitres are diagnosed correctly before operation. The demonstration of the auto-immune process has brought together a group of thyroid conditions which were formerly kept distinct on histological grounds, such as lymphocytic thyroiditis and the various subgroups of chronic non-specific thyroiditis. A great many of these cases

are difficult to differentiate from other non-toxic goitres. More important still, when a Hashimoto goitre is very firm it may be almost impossible to distinguish it from carcinoma of the thyroid by the physical signs.

However, with the laboratory methods available to us, it should be possible to make a correct diagnosis in the majority of these patients without resorting to surgery.

As repeatedly pointed out by Crile and his collaborators in recent years and as shown by Dr. Luxton's present results which we can fully support from our own experience, these goitres regress to almost normal size on administration of thyroid hormones. We find that pressure symptoms usually disappear within two months on this treatment, so that it is of great advantage to the patient not to have her thyroid removed.

The diagnostic value of the older thyroid function tests will be briefly discussed but stress will be laid on the laboratory methods arising from recent work, which include the electrophoretic separation of serum proteins, the flocculation reactions and the thyroglobulin precipitin test.

Radioiodine and B.M.R. Results

As may be expected in view of the gradual lymphoid invasion and slowly progressive destruction of the thyroid follicles by the auto-immune process, the B.M.R. and twenty-four-hour uptake of I^{131} vary according to the amount of functioning tissue left and its response to compensatory T.S.H. stimulation. In early cases both are within normal limits unless the patient has an underlying thyrotoxicosis. When the degree of thyroid destruction is such that the production of thyroid hormones decreases below normal, the output of T.S.H. is presumably increased and at that stage it is common to find an iodine uptake which is well above the normal, while the B.M.R. is still normal. Later, the gland is unable to make sufficient thyroid hormone in spite of the T.S.H. overstimulation and the B.M.R. decreases below normal, though the iodine uptake may remain high until the basal metabolism has reached myxœdematous levels. Finally, so little functioning thyroid remains that even the iodine uptake is gradually reduced below normal. Thus in patients with lymphadenoid goitre one frequently finds a marked discrepancy between the iodine uptake and the B.M.R. and the combination of these tests is more useful than each separately. The only other untreated thyroid condition in which one sees high iodine uptakes with low B.M.R.s is familial goitrous cretinism, where a congenital absence of certain thyroid enzymes leads to insufficient thyroid hormone production.

Some other parameters of iodine metabolism give results which are in keeping with the small thyroidal iodine pool to be expected in view of the extensive lymphoid replacement in the Hashimoto thyroid: the forty-eight-hour plasma radioactivity is relatively high and can be in the thyrotoxic range even in the presence of clinical myxœdema, and the biological half-life is short.

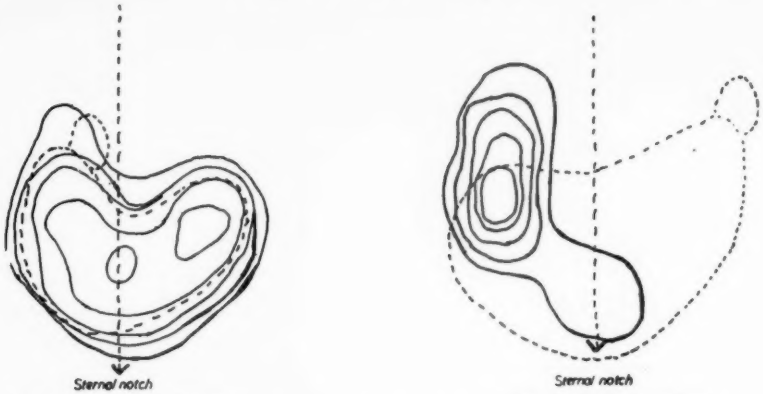
The iodine uptake cannot be increased by injections of T.S.H. since the gland is already under full stimulation, and potassium perchlorate produces a discharge of iodine in these goitres (Morgans and Trotter, 1957), owing to an interference with organic binding of which the mechanism is not yet elucidated.

From the point of view of differentiating Hashimoto's disease from carcinoma of the thyroid, however, by far the most useful test is the topographic survey of iodine distribution over the goitre area (Fig. 1), since, owing to the diffuse nature of the Hashimoto lesion, the isocount picture usually follows the outline of the palpable swelling, with more uptake on the larger side, whereas in carcinoma of the thyroid the uptake is nearly always one-sided and is absent or much diminished over the tumour.

Biochemical and Immunological Tests

The majority of untreated Hashimoto patients have abnormally high gamma globulins and as a consequence show raised values in the thymol and zinc sulphate turbidities and the colloidal gold flocculation. These serum protein changes have already been described in detail by other authors and ourselves and we propose to confine the present discussion to the correlation between the results of these tests and the demonstration of the thyroglobulin antibodies.

The details of the precipitin technique for thyroid antibodies are described elsewhere (Doniach and Roitt, 1957) and a diagram of the test is given on page 959 of the present issue (Fig. 1B, Section of Experimental Medicine). In strong sera the precipitin line becomes visible in about sixteen hours, is often double, and thickens within the next week, as increasing amounts of antibody and antigen meet and combine to form visible aggregates. When the test is done on serial dilutions of serum, the precipitin line is most compact at the equivalence zone of the system (*see* page 959, Fig. 1A, tubes 3 and 4), becoming less dense and wider in increasing dilutions, with a movement of the leading edge of the precipitate towards the serum layer. Positive precipitins were seen in up to 1/128 dilution of the serum in Hashimoto patients.



A.—J. R., female, aged 52. B.—W. V., female, aged 59.

FIG. 1.—Isocount pictures of radioiodine distribution (solid lines) to illustrate the diagnostic value of topographical surveys in differentiating between lymphadenoid goitre and carcinoma of the thyroid. Dotted lines represent extent of palpable swelling. *Case J. R.* (A), *Hashimoto's disease:* One year goitre, lassitude and lack of interest. I^{131} uptake 37%/24 hr. with symmetrical distribution. B.M.R. = +1%, E.S.R. = 23 mm. (Wintrobe), gamma globulins 2 g.% (29·7% of total), flocculation values raised. Thyroglobulin precipitin test positive, showing double line. *Case W. V.* (B), *Carcinoma of thyroid:* Two months' painful neck swelling. Large, firm, apparently diffuse goitre. I^{131} uptake 17%/24 hr., limited to right upper pole of thyroid. B.M.R. = −26%, serum cholesterol 390 mg.%, E.S.R. = 37 mm. (Wintrobe), gamma globulins 1·3 g.%, flocculation values normal.

In occasional sera the precipitate appears much more slowly, taking ten to twelve days to become visible, with a single precipitin line which is hazy and wide, and whose upper and lower edges are both fluffy. This appearance is probably not due to low antibody content, for these sera can have high gamma globulin and flocculation values, and look quite different from high dilutions of a normally precipitating serum, where the line becomes visible in two to four days and has an abrupt lower edge, however weak the antibody.

Fig. 2 shows the distribution of serum flocculation values in Hashimoto patients and

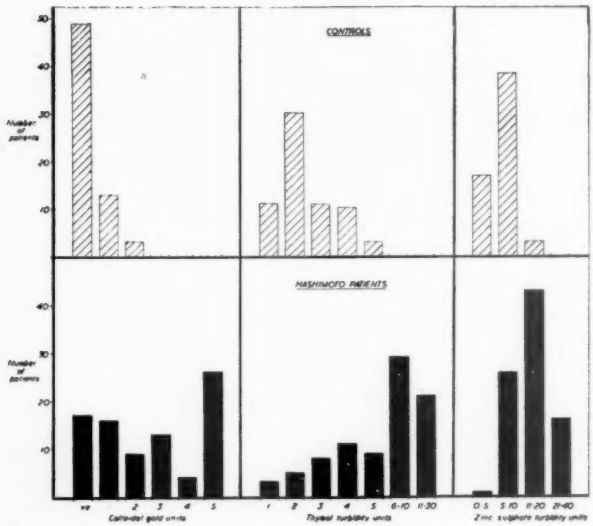


FIG. 2.—Distribution of serum protein flocculation values in Hashimoto patients treated with thyroid or untreated, and a series of controls consisting of non - toxic nodular goitres and thyrotoxics. The majority of untreated Hashimoto patients had raised flocculations. Those showing normal values were mostly treated for some years with thyroid extract. Thyroglobulin precipitins were demonstrable even after prolonged therapy.

controls. All these sera were also tested for thyroglobulin precipitins. The controls were cases of non-toxic nodular goitre and thyrotoxicosis most of whom were subsequently

verified histologically. In the Hashimoto series we included patients operated on up to three weeks before the tests since we found a lag of several months in the return of the tests to normal; patients thyroidectomized months or years previously were not included. We did not estimate the gamma globulins quantitatively in all these patients since the flocculation tests appeared to provide a more sensitive measure of the serum protein changes than the rather crude method of scanning electrophoretic strips or eluting the dye from them. The Hashimoto cases who had normal flocculation tests were mostly patients with small goitres or those treated for some years with thyroid extract and the latter generally had quite strong precipitins.

Table I shows the correlation of the serum flocculation tests with the thyroglobulin

TABLE I.—CORRELATION OF SERUM PROTEIN FLOCCULATION* TESTS AND THYROGLOBULIN PRECIPITINS IN HASHIMOTO PATIENTS

	No. of patients	+Pptins +Floccs	+Pptins −Floccs	−Pptins +Floccs	−Pptins −Floccs
Untreated	45	27	5	9	4
Treated with thyroid hormones ..	37	14	15	5	3

*Flocculation tests included thymol and zinc sulphate turbidities and colloidal gold flocculation.

precipitins. It can be seen that with the precipitin test alone, we can expect to miss about a quarter of the cases though it is on the whole more sensitive and certainly more specific than the flocculation tests. Fortunately, in many patients with negative precipitins the flocculation tests are positive and should therefore be done in every suspected lymphadenoid goitre. Some of the patients who gave negative results by both tests were early cases diagnosed only by histology. Most of them gave positive complement-fixation tests against thyrotoxic thyroid extracts as did the patients with negative precipitins and raised flocculation values.

Our finding of thyroglobulin precipitins in 4 cases of subacute thyroiditis (*see* Table II, page 960) was not altogether unexpected since thyroglobulin is known to be released from follicles damaged by the underlying virus infection in this condition (Eylan *et al.*, 1957). 2 of the cases had recovered from the acute attack and had become myxœdematous, one with persistence of the goitre, the other without thyroid enlargement. The other 2 patients were interesting in that the precipitin could be demonstrated three and five weeks after the onset of the disease. One patient has been followed up for nine months. Her precipitin titre gradually rose from 1/2 to 1/16 at five months, then slowly decreased, reaching 1/4 nine months after the acute attack. The flocculation tests were normal at first, rose to fairly high values with the rise in antibody titre, then returned to normal as these decreased again. The patient has so far remained euthyroid without substitution therapy.

The differential diagnosis between subacute thyroiditis and Hashimoto's disease can be difficult on clinical grounds since quite a few Hashimoto patients have painful goitres, and some cases of subacute thyroiditis are first seen when their acute symptoms are subsiding. Since in both conditions a high E.S.R. and evidence of thyroid auto-immunization can occur, the clinical diagnosis must be reinforced by the results of B.M.R. and iodine tests, by adequate follow up and the effect of treatment. In subacute thyroiditis the B.M.R. is often slightly raised in the presence of a complete suppression of iodine uptake by the gland, and these tests can be particularly helpful if they can be shown to return to normal as the acute stage subsides. In Hashimoto's disease the B.M.R. is more likely to be low from the start and the iodine uptake normal or high. The precipitin titre is likely to be higher in the established auto-immunization of lymphadenoid goitre, where in subacute thyroiditis it appears to be low at first, and may rise on repeated testing.

In carcinoma of the thyroid the gamma globulins are normal and the precipitin test has been negative in the few cases we have tested so far. Nodular colloid goitre is also associated with normal results on these tests unless the auto-immunization process has been grafted on a pre-existing simple goitre; in fact we have seen several patients with a history of goitre since puberty, who in middle life developed pressure symptoms fairly rapidly with a change in the size and consistency of the goitre. At operation they proved to have extensive lymphadenoid changes superimposed on colloid goitre. Two such patients had a high titre of thyroglobulin precipitins in their serum and raised flocculation values.

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Dr. A. D. Thomson (Bland-Sutton Institute of Pathology, Middlesex Hospital):

The Pathology of Hashimoto's Disease

Since the publication by Mr. Vaughan Hudson and his colleagues of the possible role of auto-sensitivity in the pathogenesis of Hashimoto's disease and the introduction of the "precipitin test" (Roitt *et al.*, 1956) as an aid to the clinical diagnosis of the disease I have had the opportunity of examining many of the thyroid glands with positive "precipitin tests". The histological features I am about to describe are based mainly on the study of this recent thyroidectomy material from the Middlesex Hospital.

Naked-eye appearances.—The enlarged thyroid gland in a typical case of Hashimoto's disease shows a smooth lobulated capsular surface which on cross section shows a replacement of the normal glistening appearance by firm homogeneous white or pink tissue traversed by fibrous trabeculæ (Fig. 1).

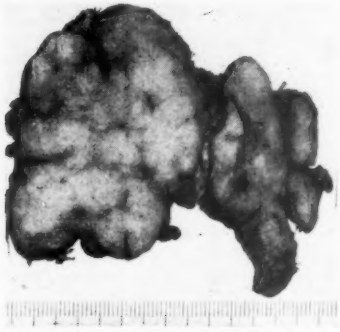


FIG. 1.—Showing the enlarged thyrcid gland in Hashimoto's disease.

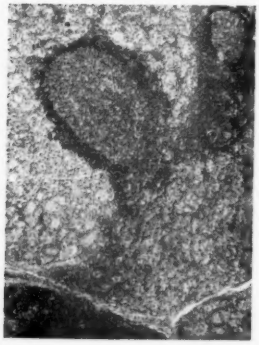


FIG. 2.—Showing the focal lymphoid tissue and the diffuse cellular infiltration between the thyroid epithelium. Colloid material is still present. Thyroid removed in 1943. × 20.

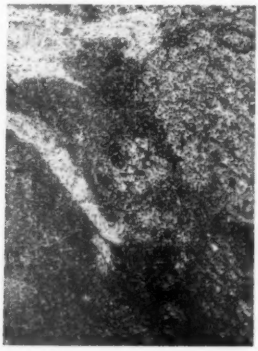


FIG. 3.—Showing a diffuse cellular infiltration between the residual thyroid epithelium. Note the absence of colloid material and the increased fibrosis. Thyroid remnant removed in 1950 from same patient as Fig. 2. × 25.

Microscopical appearances.—Histologically the features in the well-developed case are characteristic. There is a conspicuous lymphoid infiltration with prominent follicle formation (Fig. 2). The thyroid epithelial cells are abnormal in their arrangement, their cytoplasm is increased in amount and stains intensely with eosin while colloid production is impaired resulting in disorganization of the normal thyroid gland structure (Figs. 2 and 6). These epithelial changes are degenerative in nature. In addition to the lymphoid tissue with a focal distribution there is a diffuse cellular infiltration composed of lymphoctyes



FIG. 4.—Showing a colloid goitre with the cellular changes of Hashimoto's disease. × 30.

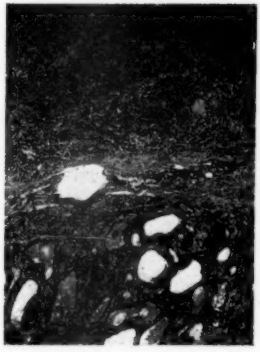


FIG. 5.—Showing a toxic goitre with the cellular changes of Hashimoto's disease. × 35.

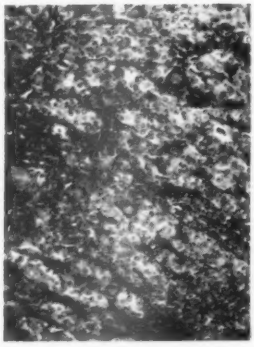


FIG. 6.—Showing the epithelial changes of Hashimoto's disease with a lymphocytic and plasma cell infiltration and many giant cells. × 75.

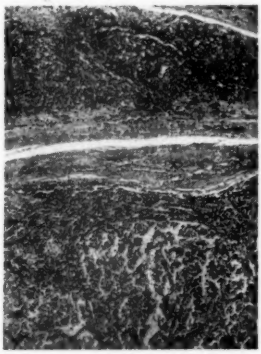


FIG. 7.—Showing Hashimoto's disease in the thyroid gland adjacent to a carcinoma. × 30.

and plasma cells which permeate between the residual thyroid epithelium. In areas this infiltrate becomes confluent and the plasma cells may exceed the lymphocytes in number. In some parts of the thyroid there is a virtual disappearance of the epithelium and the tissue is then composed of lymphocytes and plasma cells buried in fibrous tissue of varying collagenization and vascularity. As the disease progresses the cellular infiltrate and the fibroblastic tissue increase at the expense of the epithelial elements but the pathology in all cases remains confined within the capsule of the thyroid gland.

The changes I have described are found in fully developed examples of Hashimoto's disease and in these cases the "precipitin test" is positive in a high proportion of patients. A positive "precipitin test" may, however, be obtained with thyroid glands showing other histological features in addition to those already described.

(1) *Hashimoto's disease with colloid goitre.*—Some patients with a history of a goitre extending over many years develop myxœdema and the "precipitin test" proves positive. The subsequent histological examination of the thyroidectomy specimen reveals the characteristic features of a simple colloid goitre with the superimposed changes of Hashimoto's disease (Fig. 4). It appears that the long-standing clinical manifestation of an enlarged thyroid is due to the colloid goitre and the Hashimoto's disease is merely superimposed on this original pathology.

(2) *Hashimoto's disease with toxic goitre.*—A few patients have shown the classical signs

and symptoms of thyrotoxicosis with a termination in myxœdema. In these cases a thyroidectomy performed soon after this transition reveals the histological changes of Hashimoto's disease superimposed on the cellular picture of a toxic goitre (Fig. 5). Some examples with this type of pathology have a positive "precipitin test".

(3) *Giant cell thyroiditis.*—Two patients with a rapid onset of a painful goitre were diagnosed clinically as subacute thyroiditis and histological examination of the thyroidectomy specimen shows the histological changes of Hashimoto's disease with many giant cells (Fig. 6) simulating the appearance of a giant cell thyroiditis. These two examples had positive "precipitin tests".

(4) *Hashimoto's disease with thyroid carcinoma.*—An incidental finding at a recent autopsy revealed a swelling in the neck which on histological examination proved to be a papillary carcinoma with the changes of Hashimoto's disease in the adjacent thyroid gland (Fig. 7).

From this account it will be seen that the histological features of Hashimoto's disease may be superimposed on a previously normal thyroid gland, a colloid or a toxic goitre, or in the tissues adjacent to a thyroid carcinoma. In addition, when the thyroid enlargement is of more rapid onset the histology may show the lymphoid infiltration and the epithelial changes of Hashimoto's disease but containing many giant cells as described in giant cell thyroiditis.

It has been found that with a positive "precipitin test" the essential minimal histological changes are:

(*a*) Infiltration by lymphoid tissue.

(*b*) Diffuse infiltration by lymphocytes and plasma cells.

(*c*) Eosinophilic degenerative changes in the epithelium.

The subsequent progression of the pathology produces the further histological features of the fully established Hashimoto's disease. This progressive nature of the disease process can be studied when serial surgical material from the same patient is available. Fig. 2 shows the appearance of a thyroid gland partially removed in 1943 which on microscopy reveals the lymphoid infiltration and the eosinophilic degeneration of the thyroid epithelium but there is no increased fibrosis and colloid material is still visible in the thyroid vesicles. The thyroid remnant slowly enlarged during the next few years and further surgery was performed in 1950. Fig. 3 shows progression of the disease in the same patient with disappearance of the colloid, disruption and disorganization of the thyroid structure with a profuse lymphoid, lymphocytic and plasma cell infiltration of the gland with increased fibrosis.

Histologically therefore the changes in Hashimoto's disease are those of a progressive pathological process whereby an increasing amount of thyroid tissue becomes disorganized and eventually destroyed and this change may occur in a previously normal or in a previously pathological thyroid gland. The precise causation of this destructive process remains debatable but the recent demonstration by White (1957), using Coons' technique, of an antigen-antibody reaction within the thyroid gland lends support to the view of Roitt *et al.* that auto-sensitization plays a part in the pathogenesis of Hashimoto's disease.

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Section of Experimental Medicine and Therapeutics

President—Professor C. A. KEELE, M.D., F.R.C.P.

[*May* 8, 1957]

DISCUSSION ON AUTO-IMMUNITY AND THYROIDITIS

Dr. R. G. White (London Hospital):

An Immunological Investigation of Hashimoto's Disease

The demonstration by Roitt *et al.* (1956) that a precipitin reaction was given between sera of patients with Hashimoto's disease and a saline extract of normal thyroid, or a purified thyroglobulin, has given us the chance to investigate a new auto-immunization process, with the possible advantage of a defined antigen, thyroglobulin.

We of course wish to know whether the serum constituent which precipitates is really antibody, whether thyroglobulin is the antigen relevant to the process in the diseased gland, whether other antigens besides thyroglobulin are involved and so on. These are some of the questions that I have investigated at the London Hospital with the help of Professor C. F. Barwell, Dr. W. F. T. Gammie and Dr. C. R. Robinson.

The curve of inter-reaction between purified thyroglobulin, prepared for me by Dr. Ingbar by the method of Derrien *et al.* (1948) and the serum of a patient with Hashimoto's disease resembles the classical precipitin curve. When increasing amounts of antigen reacted with a constant volume of serum the amount of precipitate rose to a maximum and then fell. A test of the supernatant at optimal proportions showed an absence of both antigen and antibody. At this point subtraction of the weight of added antigen should yield the weight of antibody in the precipitate. This was 5·0 mg. per ml. of serum (neglecting the weight of complement)—an impressively high value. In other patients the curve of precipitation was more complex, with the formation of two precipitating zones, indicating the existence of at least two antibodies in the sera of patients with Hashimoto's disease.

The complement-fixation test using a saline extract of thyroid as antigen showed that complement was fixed by heat-inactivated sera of the patients with Hashimoto's disease. In general the results correlated well with the precipitin test. However, more patients (12) showed fixation than gave a precipitin test using an agar diffusion technique (8). All except 2 of those giving a positive precipitin result gave a positive complement fixation result. The situation is complicated by the existence of two zones in a titration of antigen (purified thyroglobulin) using complement fixation, and the correlation between the two serological tests requires further experience.

We have now explored the distribution of the antigenic substances in thyroid tissue relevant to the precipitin in the sera of Hashimoto patients by the fluorescent antibody technique for the localization of antigens in frozen tissue sections. Our chemical manœuvres to introduce fluorescein into the antibody of a globulin fraction of serum from a patient with Hashimoto's disease will, of course, result in the similar conjugation of fluorescein with other serum proteins. Such a fluorescein-conjugated globulin applied to a section of normal thyroid may localize to iso-antigens as well as the relevant auto-antigen. However the results were sufficiently constant with thyroid glands from a variety of sources to belittle this doubt.

Fig. 1 shows the distribution of fluorescein (bright areas) indicating the localization of the antigenic substance in a thyroidectomy thyroid (toxic goitre). The antigen which has localized the Hashimoto antibody is present within the follicles. Some variation exists between different follicles in the intensity of the fluorescence of their contents and some are void. Some antigen is also present as round globules within follicular epithelial cells.

We can get over the difficulty of iso-antigens by using our fluorescein conjugate on the thyroid sections of the same patient. Fig. 2 shows the result of such a procedure.

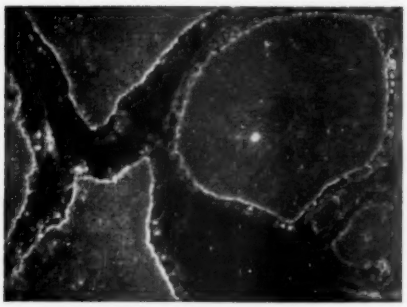


FIG. 1.—Fluorescence micrograph. Frozen section of a thyroidectomy thyroid (toxic goitre) treated with a fluorescein conjugate of the serum globulin of a patient with Hashimoto's disease. The fluorescence is localized to intra-follicular colloid and to discrete areas within the cells of the follicular epithelium. × 128.



FIG. 2.—Fluorescence micrograph. Frozen section of thyroid of a patient with Hashimoto's disease treated with a fluorescein conjugate of the patient's own serum globulin. Two follicles are lined by faintly fluorescent epithelial cells. Outside the follicles bright irregular fluorescent areas are scattered among the cells of the granulomatous infiltration, some of which show intracytoplasmic fluorescent areas. × 512.

The antigen is present within the follicles which are much reduced in size. The antigen is also present in the cells of the follicular epithelium, but there is also antigen outside these, in and among the cells of the granulomatous infiltration.

These appearances suggest that in Hashimoto's disease the antigen of the thyroid colloid freely passes from within the follicles, out, and into contact with the cells of the granuloma. It is easy, here at least, to see why antibody production should result. It does not follow that we have here the mechanism which initiates antibody production, This may well be different, but once an immune response against some element of thyroid tissue has been produced, damage to the cells may follow and this picture of escape of antigen may result. In other words, we may be witnessing how the vicious circle is kept up but not how it is initiated.

Finally, what is the source of the antibody? The histological appearances—the infiltration with plasma cells and the development of lymphoid nodules with germinal centres suggest that an antibody-producing cellular response is present in the thyroid gland itself. Another possible source of antibody is the cervical glands. In the surgical specimens from cases of Hashimoto's disease which I have examined, up to 6 lymph nodes were found closely applied to the specimens, being dissected out with them. These have been examined with a modification of the fluorescent antibody technique in order to reveal the presence of antibody (Coons *et al.*, 1955). Frozen sections treated in this way and with the necessary controls to distinguish antigen from antibody showed the peripheral lymph sinuses of the node crowded with large reticulo-endothelial cells with cytoplasmic spherical granules of antibody. The simplest explanation of this extraordinary finding is that thyroid antigen reaches the node via lymphatics and in the presence of the antibody of the lymph forms precipitates which are taken up by the sinus lining phagocytes. Also, in the medullary cords of the node were colonies of plasma cells and their precursors. Within and surrounding these was fluorescence indicating antibody.

These illustrations suggest that in Hashimoto's disease a circle of increasing immune cellular response and damage to follicular tissue is receiving prolonged stimulation from antigen continuously produced in the thyroid follicles, and we see the disease when the process is so far advanced that little follicular tissue is left and the patient is myxœdematous. Earlier stages of this process must exist, lacking circulating antibody with thyroids which still consist mainly of follicular tissue. In point of fact we have seen thyroids, which the pathology department had no hesitation in classifying as diffuse toxic goitre, in which there were small areas of lymphoid tissue and antigen in and among these cells. The sera of some of these cases had a low titre of antibody.

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Professor Ernest Witebsky (University of Buffalo School of Medicine):

Experimental Evidence for the Role of Auto-Immunization in Chronic Thyroiditis

Ehrlich and Morgenroth (1900) observed the occurrence of immune iso-antibodies against red blood cells of different individual goats. By injecting goat A with blood cells of goat B, iso-agglutinins appeared which were capable of acting upon the red blood cells of goat B and some other goats without acting upon the cells of the antibody-producing goat A. Injecting a goat with its own red blood cells never resulted in the production of auto-agglutinins. On the basis of these experimental observations, Ehrlich formulated his law of *horror autotoxicus*, implying that auto-antibodies are incompatible with normal life. This law seems to be as valid to-day as it was a half-century ago, in spite of certain important exceptions.

The unique properties of thyroglobulin as an organ-specific antigen were first recognized about thirty years ago by Hektoen and his co-workers (1927). Being engaged in the study of organ specificity of brain and lens tissue, the speaker then became immediately interested in the antigenic behaviour of thyroglobulin (Witebsky, 1929). Thyroglobulin was obtained by 50% ammonium sulphate precipitation from crude thyroid extracts of several species. Thyroglobulin antisera produced by intravenous injection reacted with the thyroglobulin used for immunization, but failed to give complement fixation with the crude thyroid extract from which the thyroglobulin was isolated. It was therefore felt that during the process of isolation this protein had become denatured. This problem has intrigued the speaker ever since, and about six years ago, collaborating with Dr. Noel R. Rose and Dr. Sidney Shulman, a practically undenatured thyroglobulin was prepared (Witebsky *et al.*, 1955; Rose and Witebsky, 1955; Shulman, 1956). This was accomplished by carefully controlling the pH, working in the cold, and using several other precautions. Antisera obtained against this purified preparation of thyroglobulin reacted quantitatively with the crude thyroid extract from which it was isolated. Conversely, antiserum obtained against crude thyroid extract reacted equally well with its isolated thyroglobulin fraction.

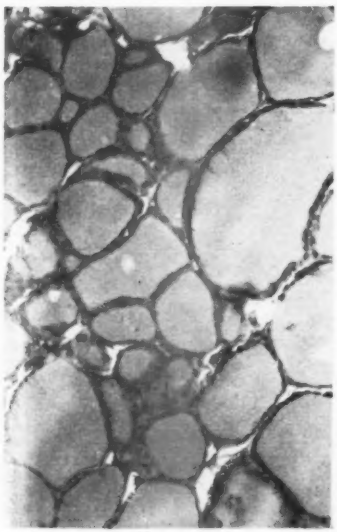


FIG. 1.

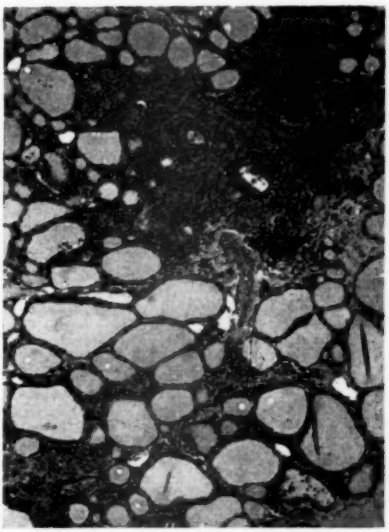


FIG. 2.

FIG. 1.—Thyroid gland of normal rabbit fixed in buffered formalin and stained with hæmatoxylin and eosin (× 95).

FIG. 2.—Rabbit 294: Injected with pooled rabbit thyroid extract (with Freund adjuvants) intraperitoneally on December 28, 1954, and February 22, 1955. Thyroids removed April 11, 1955. The photograph shows one of the numerous areas densely infiltrated by lymphocytes and eosinophils. The follicles in these areas are compressed and contain little colloid. The original follicular pattern is seen along the borders of the infiltration, although even there some cellular desquamation and exudation into the colloid can be seen.

We subsequently used crude thyroid extracts and isolated thyroglobulin almost interchangeably in all our experiments.

Crude thyroid extracts, initially containing as much as 60%–80% thyroglobulin, seemed to present a good instrument to challenge the validity of the *horror autotoxicus* law. These experiments were carried out in the belief that we could substantiate rather than disprove it. The experimental results of this undertaking, however, proved surprisingly different. About one-third of the rabbits injected intradermally with pooled rabbit thyroid extracts incorporated in Freund adjuvants produced circulating antibodies demonstrable by complement fixation and precipitation (Witebsky and Rose, 1956; Witebsky *et al.*, 1956). The percentage of rabbits with detectable circulating thyroid antibodies in their blood stream could be increased considerably by using the tanned cell hæmagglutination test introduced by Boyden (1951). Tanned rabbit cells or human cells of Group O when coated with rabbit thyroid extract were agglutinated by the serum of immunized rabbits sometimes in dilutions as high as several thousand. The tissue specificity of these antibodies was proven by testing various rabbit organ extracts by complement fixation. Only the thyroid extracts, and not the extracts of other organs, gave positive reactions. To exclude further the possible interference of iso-antibodies, rabbits were thyroidectomized and injected with extracts of their own thyroid gland. Again, even under these conditions thyroid antibodies appeared, strongly suggesting that one was dealing with a true auto-antibody, and not an iso-antibody.

It took us some time, as a matter of fact several months, before we became curious enough to find out what happened to the thyroid glands of normal non-thyroidectomized rabbits which had developed circulating thyroid antibodies following injection of pooled rabbit thyroid extract (Rose and Witebsky, 1956). Fig. 2 shows typical changes observed in the architectural structure of the thyroid glands in one of these animals, as compared with a section of a normal rabbit thyroid gland (Fig. 1). These histological alterations, which were sometimes even more extensive than the illustration shows, furnished further evidence for the auto-antibody nature of the antibodies produced. We are forced therefore to conclude that certain constituents of the thyroid gland, presumably

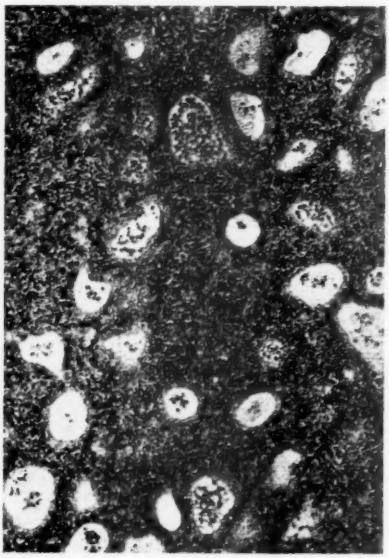


FIG. 3.

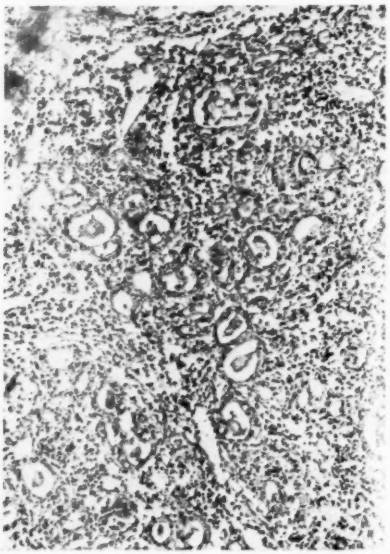


FIG. 4.

FIG. 3.—Dog 1196: Injected with pooled dog thyroid extract (with Freund adjuvants) on September 20, 1954, December 24, 1954, and January 28, 1955. Thyroid removed May 23, 1955. The photograph shows a dense infiltration of lymphocytes with a somewhat nodular arrangement. Most of the follicles contain leucocytes and desquamated epithelium with very little colloid remaining.

FIG. 4.—Patient Tho, chronic thyroiditis.

thyroglobulin, are potentially true auto-antigens. In addition, the auto-antibodies produced can act upon the normal thyroid gland of the antibody-producing animal itself, causing an experimental thyroiditis. Similarly, dogs and guinea-pigs were treated with pooled extracts of their own species in exactly the same manner as the rabbits. A section through the thyroid glands of one of these dogs is shown in Fig. 3. Again, considerable changes are apparent in the thyroid gland in spite of the fact that in this case no antibodies were demonstrable in the serum. In dogs and guinea-pigs the correlation between circulating antibodies and the histological changes was not as marked as in the case of the rabbits. The question then arises as to whether the circulating antibodies *per se* are responsible for the tissue changes or whether other types of antibodies, such as the cell-bound antibodies, might actually be the agents responsible for the tissue damage in the immunized animals. Indeed, skin tests performed on immunized rabbits gave positive reactions of the delayed type, which again were specific and limited to rabbit thyroid extract rather than to the extracts of other rabbit organs. In examining the sections of the thyroid glands of animals immunized with pooled thyroid extracts of their own species, the similarity to certain diseases of the human thyroid becomes obvious. Unfortunately, it has taken us quite some time to collect a sufficient number of sera, as our hospital has no special thyroid clinic. Roitt *et al.* (1956), in a preliminary communication, reported that they found precipitins directed against thyroid extract in the serum of patients with so-called Hashimoto's disease. Using exactly the same techniques as applied in the serological examination of experimental animals, we also found a considerable number of patients with antibodies directed against human thyroid extract. From the serological point of view, the tanned cell hæmagglutination test in our hands was found to be considerably more sensitive than the precipitation test. The tanned cell hæmagglutination test permits us to detect thyroid antibodies in the serum of many patients which failed to give precipitation. Incidentally, the complement-fixation test in human cases of thyroiditis proved the least satisfactory.

I should like to present an example of a patient (Tho) having thyroiditis (Fig. 4) whose serum contained both precipitins and antibodies demonstrable by the tanned cell hæmagglutination test, as well as another case (Bur) of thyroiditis (Fig. 5) where the tanned cell hæmagglutination test alone allowed the recognition of thyroid antibodies (Table I).

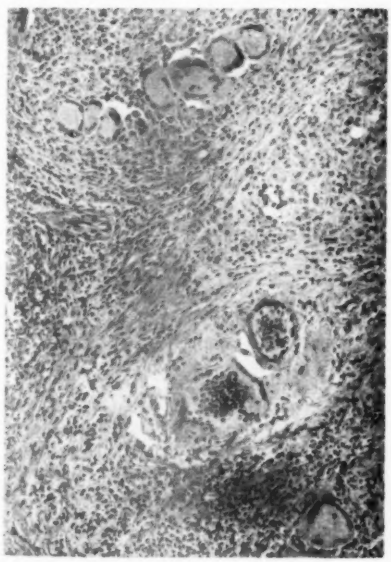


FIG. 5.—Patient Bur, chronic thyroiditis (granulomatous type).

TABLE I

A. Hæmagglutination Test

Dilutions of patient's serum	Patient Tho	Patient Bur
1 : 3	+++	+++
1 : 9	+++	+++
1 : 27	+++	+++
1 : 81	+++	+
1 : 243	+++	–
1 : 729	+	–
1 : 2187	+	–
1 : 6561	–	–
Uncoated cells	–	–

B. Precipitation Test

Dilutions of human thyroid extract	Patient Tho	Patient Bur
Undiluted	+	–
1 : 10	+++	–
1 : 100	+	–
1 : 1000	–	–
saline	–	–

"+++" to "–" indicate the various degrees of agglutination or precipitation respectively.

A, Human erythrocytes (Group O) were treated with highly diluted tannic acid and coated with heated human thyroid extract. The cells were added to serum dilutions and agglutination determined after overnight incubation at 4° C. (*see* Witebsky and Rose, 1956).

B, Undiluted, active patient's serum added to dilutions of human thyroid extract. Amount of precipitate graded after overnight incubation at 4° C. (*see* Witebsky *et al.*, 1955).

Our papers on chronic thyroiditis and auto-immunization (Witebsky *et al.*, 1957*a*, *b*) dealing with the further correlation of experimental and human thyroiditis will be published in the near future.

In investigations of this type it is important to exclude the possibility that the antibody involved is an iso-antibody directed against a group specific antigen present in the tissues of some human beings and not in others. To exclude this possibility, hæmagglutination tests were set up using as antigens thyroid extracts from 14 different individuals. In each case a reaction was obtained with essentially identical titre. In addition, attempts were made to inhibit the reaction of a thyroiditis serum with human thyroid extract by adding extracts of human liver, spleen, kidney, gastric mucosa, and serum to the patient's serum before the tanned and coated cells were added. Thyroid extract was the only one to inhibit the reaction at all. All this evidence indicates that the antibody involved is a specific thyroid antibody rather than an iso-antibody of any sort.

In the case of thyroiditis we are therefore facing an interesting situation. Extracts prepared of an animal's own thyroid gland proved to be antigenic for the individual animal itself. Undoubtedly therefore we are dealing with a true auto-antigen, presumably thyroglobulin, which produces antibodies capable of acting upon the normal thyroid tissue of experimental animals. The equivalent in humans is seen in certain kinds of chronic thyroiditis, where apparently a constituent of the patient's own thyroid gland becomes antigenic, for reasons yet unknown. Chronic thyroiditis then, I believe, is a clear-cut example in which auto-immunization has been proven to play a major role in the pathogenesis of the disease, substantiated by reproducible evidence in experimental animals.

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Dr. I. M. Roitt and Dr. Deborah Doniach (Courtauld Institute of Biochemistry and Institute of Clinical Research, Middlesex Hospital Medical School):

Auto-immunization in Thyroid Diseases

The finding of raised gamma globulins and abnormal serum protein flocculation results in Hashimoto's disease, their gradual return to normal after removal of the goitre (Luxton and Cooke, 1956; Skillern *et al.*, 1956; Doniach and Hudson, 1957) as well as the infiltration of the thyroid gland with antibody-producing cells, led us to postulate that these changes were due to an immune process directed against the thyroid. The sera of patients with this type of goitre were found to contain precipitating antibodies against human thyroglobulin (Roitt *et al.*, 1956).

The thyroglobulin precipitins were demonstrated by double diffusion in agar using a modified Oudin technique (Doniach and Roitt, 1957) (Fig. 1).

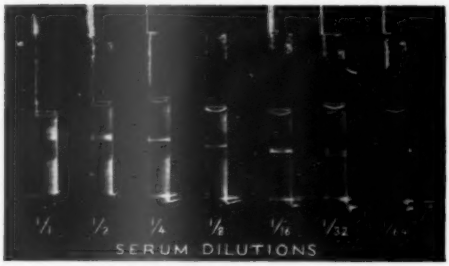
The antibody was proved to be specifically directed against thyroglobulin, negative results being obtained against extracts of other human tissues. The precipitins were equally demonstrable when crude thyroid extracts from normal or thyrotoxic glands were used. The antibody furthermore showed a narrow species specificity.

Localization of the precipitating antibody in the gamma globulins was demonstrated after fractionation of the patient's serum by zone electrophoresis on cellulose columns and by immuno-electrophoresis.

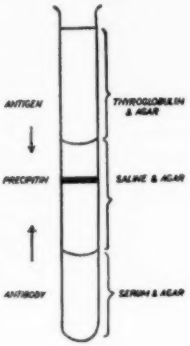
A proportion of sera gave a double precipitin line (Fig. 2) and this was shown to be due to the presence of two immunologically distinct proteins in the thyroglobulin preparation.

Quantitative studies (Heidelberger and Kendall, 1935) done with purified thyroglobulin showed that the sera of some patients contained as much as 5 mg. of antibody protein per ml. Two types of precipitin curves were seen in different patients; one type resembled the rabbit precipitating system with complete precipitation in antibody excess, while the other was more akin to the curve obtained with horse flocculating antibody, showing partial or almost complete solubility of the antibody-antigen complex in excess antibody.

By using radioactive thyroglobulin it was possible to show that the ratio of antibody to



A



B

FIG. 1.

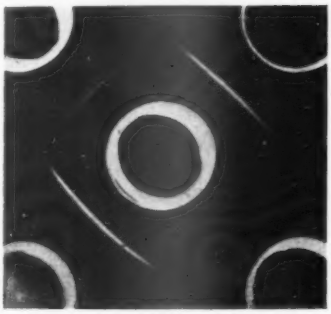


FIG. 2.

FIG. 1A.—Thyroglobulin precipitin test done on serial dilutions of serum from a Hashimoto patient, using 5 mg./ml. thyroglobulin as the antigen. Precipitins were visible to 1/64 dilution of the serum. The compact band seen in 1/4 and 1/8 tubes indicates equivalence of antibody and antigen. The leading edge of the precipitate approaches the serum layer with progressive dilution.

FIG. 1B.—Demonstration of thyroglobulin precipitins: the Oudin technique. The antigen and antibody diffuse towards each other in the neutral zone. A precipitate occurs when they meet in suitable proportions.

FIG. 2.—Precipitin reaction done by the Ouchterlony agar diffusion technique. Central well contained 5 mg./ml. thyroglobulin solution. 4 different Hashimoto sera were placed in the peripheral wells. One of these shows a double precipitin line.

antigen in the specific precipitate varied from 4 : 1 in the region of antibody excess to 2 : 1 in the zone of antigen excess. These ratios are considerably lower than those found in studies with the rabbit antibody against hog thyroglobulin (Heidelberger, 1938), where values of up to 40 : 1 have been obtained and this may be related to the narrower specificity of the auto-antibody.

Results of the thyroglobulin precipitin test: A total of 107 Hashimoto sera were examined by the precipitin test (Table I). Seventy of these patients were either untreated or treated

TABLE I.—THYROGLOBULIN PRECIPITIN REACTIONS IN HASHIMOTO PATIENTS

	No. of cases	
	Positive	Negative
Untreated .. .. .. } Treated with thyroid hormones }	52	18*
Post-operative	14	23

*5 Doubtful diagnosis.

with thyroid hormones without surgical removal of the goitre and of these 52 gave positive precipitins and 18 were negative. All but one of the sera which were negative by the precipitin test gave positive results when tested by complement fixation, using extracts of thyrotoxic gland as the antigen (Trotter *et al.*, 1957). The serum which was negative by both methods was further studied by a more sensitive precipitin method using radioactive thyroglobulin and rabbit-antihuman-gammaglobulin serum. By this means the patient was shown to have some antibody, but in amounts insufficient to give a visible precipitate by the Oudin technique. Of 37 post-operative Hashimoto patients tested, only 14 gave positive precipitin tests, the incidence of negative results increasing with the amount of thyroid tissue removed and the length of time elapsed since the operation.

The sera of 238 patients with other thyroid diseases were examined by the precipitin test. Results are shown in Table II. None of the patients with thyrotoxicosis or non-toxic nodular goitre had any precipitins but the sera of two thyrotoxic patients, who developed myxœdema following thyroidectomy and I^{131} respectively, contained complement-fixing

antibodies. Quite strong precipitins were found in 6 patients with primary myxœdema without goitre and in 4 cases of subacute thyroiditis. The only case of true Riedel's disease tested was negative by the precipitin test, though her serum contained weak complement-fixing antibodies.

TABLE II.—THYROGLOBULIN PRECIPITIN REACTIONS IN OTHER THYROID DISEASES

	Number of cases	
	Positive	Negative
Thyrotoxicosis:		
Active or in remission after Neo-Mercazole	0	68
Post-thyroidectomy or post-I^{131}:		
Euthyroid	0	20
Myxœdema	0	17
Non-toxic nodular goitre	0	103
Myxœdema without goitre	6	27
Subacute thyroiditis	4	2
Riedel's thyroiditis	0	1
		238

The ætiology of Hashimoto's disease.—The demonstration of circulating antibodies against the patient's own thyroid gland in chronic thyroiditis and the known cytotoxic effects of experimentally induced auto-immunization suggested that the disease might arise by a self-perpetuating destructive process depending upon an immune response to thyroglobulin or some other protein in the thyroid gland. Since thyroglobulin is normally confined in the follicles and does not circulate freely, individuals will not have acquired an immunological tolerance to it (Medawar, 1956).

It is of considerable interest that Witebsky and Rose (Rose and Witebsky, 1956; Witebsky *et al.*, 1957) have succeeded in immunizing several animal species against extracts of homologous thyroid glands and have observed lesions in the thyroids of animals so treated which have many features in common with human chronic thyroiditis. Thus it can be supposed that in the human subject, any release of thyroglobulin from the follicle could elicit an auto-immune response and stimulate invasion of the gland by lymphoid elements with local antibody production, causing possible damage to adjacent follicles with further release of colloid. In time the thyroid gland may become diffusely involved and distant parts of the reticulo-endothelial system may be implicated in the production of antibodies. The unusually high level of circulating antibody in these patients is a reflection of this hyperimmunization, probably resulting from prolonged and continuous leakage of antigen from the gland.

Classical Hashimoto's disease represents a late and extreme example of this process. When the glandular elements are almost completely destroyed and the antigenic stimulus has diminished, it is conceivable that the lymphoid elements regress, leaving a fibrotic thyroid gland which, if judged on histological grounds only, may be indistinguishable from Riedel's thyroiditis. However, true invasive fibrous thyroiditis as defined by rigid operative and clinical criteria (Woolner *et al.*, 1957) may be a distinct condition though the finding of weak complement fixation by the serum of our patient who answered these criteria cannot be disregarded. It was kindly tested for us by Dr. R. G. White and independently by Dr. G. Belyavin, with concordant results. Dr. White also tested this serum against the extracts of other human organs but was only able to detect weak antibodies against the thyroid.

The finding of precipitins in the sera of patients with primary myxœdema without goitre accords well with the frequent lymphoid infiltration found in the small fibrotic glands of myxœdematous subjects. It is likely that the development of a goitre as a result of thyroid auto-immunity depends on the ability of the gland to respond to T.S.H. Similar wide individual variations exist in the goitrogenic reactions of thyrotoxic patients treated with antithyroid drugs: in some cases, over-treatment to the point of hypothyroidism produces no enlargement of the goitre, whereas in a few subjects, the slightest overdosage gives rise to a marked goitrogenic effect.

It appears that thyroid auto-immunity is not always progressive since the majority of patients with subacute thyroiditis recover without sequelæ despite the finding that thyroid precipitins can be present quite early on in the disease. It may be that the mere release of thyroglobulin and the development of precipitins against it are insufficient to perpetuate the damaging chain reaction in the thyroid gland and that a cellular hypersensitivity of an as yet unknown nature is involved.

We are grateful to Mr. R. Vaughan Hudson for his co-operation and interest and to Dr. P. N. Campbell for helpful discussion.

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Dr. W. R. Trotter, Dr. G. Belyavin and Dr. A. Waddams (University College Hospital Medical School):

Precipitating and Complement-fixing Antibodies in Hashimoto's Disease

Since the publication of Roitt and Doniach's preliminary report (Roitt *et al.*, 1956), we have examined the sera of a number of cases of thyroid disease, using the agar gel technique for detecting precipitating antibodies. The antigen employed in these tests was a simple saline extract made from slices of normal thyroid obtained at post-mortem. The results obtained were extremely similar to those described by previous speakers, so I shall not refer to them in detail.

We have also looked for complement-fixing antibodies in the serum of cases of Hashimoto's thyroiditis. The initial results were uniformly negative even with sera in which precipitating antibodies were easily demonstrable. At that stage we had a most informative discussion with Dr. White, in which he told us that he had been able to obtain complement fixation in several cases of Hashimoto's thyroiditis. His antigen, however, was derived from a thyroid obtained at operation from a case of thyrotoxicosis, whereas ours came from a normal thyroid obtained at post-mortem. We therefore made a saline extract from a thyrotoxic thyroid and found that this fixed complement when set up against sera from all our proved cases of Hashimoto's thyroiditis (using a method of complement fixation described by Belyavin (1953) and 2 M.H.D. of complement).

Table I gives some examples of the antigens we have used. Sera containing precipitating

TABLE I.—THYROID EXTRACTS USED AS ANTIGENS

Number examined	Type of thyroid	Source	Precipitating activity	Complement-fixing activity
4	Normal	Post-mortem	+	−
1	Normal	Operation	+	−
2	Nodular goitre	Operation	not tested	−
4	Toxic diffuse goitre	Operation	+	+

antibodies have given consistently positive precipitin tests against all the thyroid extracts so far tested; but complement-fixation has been obtained only against the extracts of the four thyrotoxic thyroids. This does not seem to be because they were obtained fresh at operation, because a normal thyroid obtained in the same way was negative. Thyroglobulin, which was most generously supplied by Dr. Roitt, has been tested in dilutions varying from 0·5 to 8·0 mg. per ml., and the results have been consistently negative against a range of sera known to contain complement-fixing antibodies.

Table II shows the results of a preliminary attempt at separation by high-speed centri-

TABLE II

Procedure	Precipitin titre	Optimal C.F.T. titre
Homogenized Thyroid		
Untreated	1 : 80	1 : 20
Centrifuged at 11,300 *g* for ½ hour ..	1 : 80	1 : 10
Centrifuged at 20,500 *g*	negative	negative
Centrifuged at 105,400 *g*	negative	negative
Saline Extract of Thyroid Slices		
Untreated	1 : 80	1 : 5
Centrifuged at 20,500 *g* for 1 hour ..	1 : 40	negative

fugation. Two different extracts of the same thyrotoxic gland were used. Both were of the same strength (20% w/v), but in one instance the thyroid was homogenized whereas in the other it was sliced and left in contact with saline for twenty-four hours. Some differences can be observed between the precipitating and complement-fixing antigens. The amount of precipitating antigen was about the same in both extracts; but there was much less complement-fixing antigen in the extract of the slices. Centrifuging the homogenate at 11,300 *g* got rid of some of the complement-fixing activity, but precipitating activity was unchanged. Centrifuging at 20,500 *g* eliminated both antigens from the homogenate. When the extract of the slices was centrifuged at this speed the supernatant contained precipitating, but not complement-fixing activity.

Table III summarizes the results obtained to date by testing sera from a number of

TABLE III

Diagnosis	Number of cases	Precipitin + ve	C.F.T. + ve
Normal	21	0	1
Simple goitre	18	0	0
Proved Hashimoto.. ..	10	4	10
Probable Hashimoto ..	14	8	12
Spontaneous myxœdema ..	9	3	5
Thyrotoxicosis	10	0	4

different thyroid diseases. It will be seen that the complement-fixation test has been positive in all except 2 patients with Hashimoto's disease. In the 2 negative cases the diagnosis has not been proved histologically. The precipitin test has been less consistently positive, even in unoperated cases.

The number of normal subjects tested so far is exceedingly small and as one of these gave a positive complement-fixation test we cannot claim that this test is necessarily specific for thyroid disease. On the other hand the cases of simple goitre have so far been consistently negative.

It is not very surprising to find that a proportion of cases of spontaneous myxœdema has reacted positively to both tests. When extreme atrophy has not occurred, the histology of the thyroid in this condition is remarkably similar to that seen in Hashimoto's thyroiditis. Patchy lymphadenoid change is likewise seen in some toxic goitres, so that again it is not surprising that occasional positive results have been obtained in thyrotoxicosis. It is of some interest to note that one thyrotoxic patient, whose thyroid had been shown to contain the complement-fixing antigen, did not have demonstrable complement-fixing antibodies in her serum.

The present work is at an embryonic stage, and some obvious control experiments have not yet been performed. For instance we have not as yet examined organs other than the thyroid for the presence of complement-fixing antigen. Similarly we have not examined serum from patients with non-thyroid disease for complement-fixing antibody. The specificity of the complement-fixation test is therefore as yet quite unproved. But even at this early stage in the investigation we feel that certain preliminary conclusions can be cautiously advanced. On the one hand we have evidence that certain thyrotoxic thyroids contain a substance which behaves like an antigen in the complement-fixation test. All we can say about this substance at present is that it does not appear to be thyroglobulin. On the other hand we have evidence that corresponding antibodies are present in serum from almost all cases of Hashimoto's thyroiditis, most cases of spontaneous myxœdema, some cases of thyrotoxicosis and occasional normal subjects. It is known that lymphadenoid change is universal in Hashimoto's thyroiditis, usual in spontaneous myxœdema, not infrequent in thyrotoxicosis and occasionally found in normal thyroids. It is possible therefore that there is a correlation between lymphadenoid change and the presence of complement-fixing antibodies; but at the moment this correlation is still hypothetical. The most hopeful aspect of the present work would appear to be that it provides an opportunity for learning something of the mechanisms involved not only in Hashimoto's thyroiditis, but also in thyrotoxicosis.

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[*June* 7, 1957]

DISCUSSION ON THE PENETRATION OF DRUGS INTO THE CEREBROSPINAL FLUID

Dr. **Hugh Davson** (Medical Research Council, Department of Physiology, University College):

Physiological Aspects of the Penetration of Drugs into the Cerebrospinal Fluid

The problem of the penetration of drugs into the cerebrospinal fluid is just one aspect of the more general problem of the nature of the barriers between blood, on the one hand, and the cerebrospinal fluid and central nervous tissue on the other, i.e. the so-called blood-C.S.F. and blood-brain barriers. When a substance is injected into the blood it finds its way rapidly into the extracellular fluids of most parts of the body; in the central nervous system, however, this penetration is usually much slower, so slow indeed with some substances that their presence cannot be detected either in the cerebrospinal fluid or in the central nervous tissue even after some hours. It is this phenomenon that has given rise to the concept of a barrier that slows down the passage of material from blood to the cerebrospinal fluid and nervous tissue. We must consider first, then, the anatomical pathways available for penetration from blood to cerebrospinal fluid. It is believed that the fluid is elaborated as a secretion of the epithelium of the choroid plexuses of the ventricles; the fluid is formed continuously, passes into the cisterna magna and thence through the rest of the subarachnoid spaces at the base and over the convexities of the brain, to be drained away into the dural sinuses. If the substance we are considering, for example a sulphonamide, is able to enter the secretory cells of the choroidal epithelium, we may expect it to appear in the primary secretion of cerebrospinal fluid and flow with it over the surface of the brain; if we maintain a constant concentration of the drug in the plasma over a long period we may therefore expect the concentration to rise in the cerebrospinal fluid continuously; it will rise more rapidly in the ventricles than in the subarachnoid fluid, and we may expect the subarachnoid fluid of the spinal cord to lag behind the fluid elsewhere if circulation of fluid here is less continuous and rapid. Experiments show, however, that there is another possible route of penetration from blood to cerebrospinal fluid; this is by way of the capillaries of the nervous tissue, into the extracellular space of the tissue and thence into the ventricles and subarachnoid space. In other words, penetration into the cerebrospinal fluid may involve passage through the *blood-brain barrier*. For convenience, we may describe the blood-C.S.F. barrier as the barrier between blood and C.S.F. in the ventricles, i.e. the epithelium of the choroid plexuses; the blood-brain barrier becomes the barrier between the capillaries of the nervous tissue and the extracellular fluid of this tissue—it may be the capillary endothelium or it may be the so-called pia-glial lining supposed to cover this endothelium.

In general, physiological experiments have shown that these two barriers are very similar, in the sense that if a substance passes rapidly into the one compartment, e.g. the cerebrospinal fluid, then it also passes rapidly into the other. As with cellular permeability it is essentially the degree of lipoid-solubility of the substance that determines its ability to cross the barrier; thus alcohol and urethane pass so rapidly that it is difficult to measure the rate at which the blood comes into equilibrium with the cerebrospinal fluid after an intravenous injection of either of these substances. It is for this reason that many sulphonamides pass readily into the cerebrospinal fluid; thus sulphapyridine and sulphanilamide have high lipoid-solubility and appear rapidly in the fluid after an intravenous injection. Sulphadiazine and sulphathiazole have lower lipoid-solubilities and penetrate more slowly. Penicillin has a very low lipoid-solubility and it is difficult to detect its penetration; Chloromycetin is quite lipoid-soluble and penetrates easily. In general, if a drug has a partition coefficient—Concn. in Oil/Concn. in Water—greater than that of sulphadiazine, namely 0·035, we may expect it to penetrate sufficiently rapidly to permit of its therapeutic use.

So much for the general problem; some particular aspects that may have an important bearing on the choice of a drug are as follows:

Different regions of the cerebrospinal system.—As indicated above, the ventricles may be considered to be the most favoured with regard to coming into equilibrium with the blood plasma. This is found to be true in practice, the lumbar fluid lagging well behind the cisternal fluid. The discrepancy becomes small, however, with substances that penetrate very rapidly. Thus, if a substance penetrates with some difficulty, e.g. sulphadiazine, then we may expect the concentration in the lumbar fluid to be much less than that in the ventricles.

The abnormal barrier.—In meningitis it is considered that the barrier between blood and cerebrospinal fluid is broken down; presumably the blood vessels of the pia mater allow material to escape into the subarachnoid fluid. Under these conditions drugs that were unable to cross the barrier in the normal subject do penetrate the cerebrospinal fluid in measurable amounts.

Measurement of drug penetration.—For results to be of general value it is desirable that the concentration of the drug in the blood plasma be measured at intervals during the penetration of the drug into the cerebrospinal fluid. Thus, if a single intravenous injection is given, and blood is sampled say one, fifteen, thirty and sixty minutes later and the cerebrospinal fluid just once at sixty minutes, it is possible to compute a transfer constant that permits comparison with other values. It is worth noting, also, that the blood-aqueous barrier, i.e. the impediment to penetration from blood into the aqueous humour of the eye, is very similar to the blood-cerebrospinal fluid barrier. If it is known that a drug penetrates rapidly into the aqueous humour it can be accepted that it will also penetrate rapidly into the cerebrospinal fluid.

Dr. Honor V. Smith (Department of Neurology, Radcliffe Infirmary, Oxford):

The fact that certain substances normally present in blood, or artificially introduced into the blood stream, either do not appear in the cerebrospinal fluid (C.S.F.) or do so only in minute amounts is one that has an important bearing on both the pathogenesis and treatment of certain neurological diseases. Dr. Davson has discussed the basic physiological problems of this blood-C.S.F. barrier, and I shall attempt to describe briefly certain studies carried out in recent years in Oxford, and to consider some of their clinical implications.

Of the substances we have studied, the first in clinical importance are those used in the chemotherapy of neurological infections. It is now established that, when the meninges are normal, none of the usual chemotherapeutic agents except the sulphonamides and iso-nicotinic acid hydrazide (I.N.A.H.) will enter the C.S.F. in anything except negligible quantities. It is, however, widely held that inflammation of the meninges greatly increases the permeability of the barrier, and that therefore penicillin or streptomycin, when given systemically in cases of active meningitis, will appear in the C.S.F. in therapeutic concentrations. This important assumption clearly requires careful verification. Unfortunately penicillin and streptomycin are not themselves ideal indicator substances to use in studying the effects of inflammation and other conditions on the permeability of the blood-C.S.F. barrier, since they can only be estimated quantitatively by biological methods that, of necessity, carry a considerable margin of error.

We have, therefore, studied the partition of bromide, magnesium and calcium between blood and C.S.F. in a large variety of neurological conditions. These are all substances that can be accurately estimated in body fluids even in very low concentrations (Hunter, 1955; Hunter and Stott, 1956). In many cases, too, we have studied the rate of passage of radioactive sodium, Na^{24}, from blood to C.S.F. Much of this work is still at an early stage, but we have already found consistent departures from the normal in old age, in diseases of the basal nuclei such as Parkinson's disease, and in inflammatory conditions of the nervous system (Bourdillon *et al.*, 1957). It is with these last that I am particularly concerned to-day.

Cohen's law.—Earlier workers have found that in active meningitis substances normally present in higher concentration in blood than C.S.F. increase their concentration in the C.S.F., whereas those that are normally at a higher concentration in the C.S.F. decrease (Cohen, 1924). This generalization is sometimes known as Cohen's law. It may be expressed by saying that whatever the normal ratio of the C.S.F. concentration to that of the serum, this ratio is altered in meningitis in the direction of unity. Table I shows the

TABLE I

	Magnesium		Calcium		Bromide	
	No. of cases	C.S.F./S.	No. of cases	C.S.F./S.	No. of cases	C.S.F./S.
"Normal"	17	1·35	13	0·51	34	0·39
Tuberculous meningitis	15	0·94	13	0·64	15	0·96

mean values for the ratio of C.S.F. to serum concentration for magnesium, calcium and bromide, in 15 cases of active tuberculous meningitis compared with 17 so-called "normals". These latter were cases in which lumbar puncture was indicated in the course of their investigation, but where no evidence of progressive neurological disease was found.

In broad outline these findings conform to Cohen's law. Thus, with calcium, where normally the concentration in the C.S.F. is only about half that of serum, in tuberculous meningitis the C.S.F. concentration increases so that the ratio of C.S.F. to serum rises. Magnesium, on the other hand, is normally present in higher concentration in C.S.F. than blood; and the effect of the meningitis is to lower the ratio. Cohen, discussing the alteration of the chloride distribution in meningitis, stated that he never found the C.S.F. chloride concentration to fall below that of the serum, but, as our figures show, the magnesium

ratio can actually be reversed. This effect may be even more marked with the bromide ratio. Although in the normal the C.S.F. concentration is only about one-third that of blood, in active tuberculous meningitis not only are ratios of the order of unity the rule, but on occasion they may be as high as 1·4.

Tuberculous meningitis as opposed to other varieties of meningitis.—It cannot, however, be assumed that similar results will be obtained in all types of meningitis, irrespective of their ætiology. On the contrary, experience has shown that the blood-C.S.F. barrier is more profoundly and more consistently affected in tuberculous meningitis than in other varieties of meningitis showing comparable changes in the C.S.F. The difference is indeed sufficiently well marked to serve as the basis of a useful diagnostic test (Hunter *et al.*, 1954).

The one other condition in which the effect on the barrier seems to be consistently of the same order as in tuberculous meningitis is neoplasia of the meninges. Thus, although in cases of brain tumour as a whole the bromide ratio has been normal, in 2 cases of oligodendrogliomatosis and one of carcinomatosis of the meninges the ratio was unity.

The effects of a specific inflammation on the blood-C.S.F. barrier.—It is clear, then, that except in the most general terms, no rule can be formulated as to the result of meningeal inflammation as such on the permeability of the blood-C.S.F. barrier. But not only does the effect on the barrier vary with the ætiology of the inflammation: we have evidence that the effect of a given inflammation is not necessarily the same for all substances. This is well seen when the effects of the intrathecal tuberculin reaction of the blood-C.S.F. barrier are considered (Smith *et al.*, 1955). By the intrathecal tuberculin reaction is meant the transient wave of sterile meningitis that follows the introduction of tuberculin into the spinal fluid of a subject sensitized to tuberculin. We have used intrathecal tuberculin in the treatment of various diseases; and since, on the whole, the changes provoked in the C.S.F. have proved remarkably constant in both occurrence and pattern, we have taken advantage of these reactions to study the effects of a given inflammation on the permeability of the blood-C.S.F. barrier.

Systemic versus intrathecal tuberculin.—In the first place, the barrier to tuberculin itself appears to be absolute. In the sensitized guinea-pig the cisternal injection of tuberculin is followed by an intense inflammation involving not only the meninges but also the perforating vessels of the neuraxis (Bosanquet *et al.*, 1953). If, however, a fatal dose of tuberculin is given by intraperitoneal injection, no significant meningeal exudate is found *post mortem*. In man, intramuscular tuberculin, when given as an adjuvant to the chemotherapy of systemic tuberculosis, produces no concomitant changes in the C.S.F.; nor is the passage of either penicillin or bromide from blood to C.S.F. in any way affected (Swithinbank *et al.*, 1953; Fig. 13).

Changes with intrathecal tuberculin.—Contrast this with the effects of tuberculin when given as the Purified Protein Derivative, P.P.D., directly into the cerebrospinal fluid of a highly sensitized subject (Smith *et al.*, 1955; Fig. 1). Twenty-four hours after an injection of 3·75 mg. of P.P.D. the C.S.F. typically contains many hundreds or, more commonly, thousands of cells and the protein content is also markedly increased. Both the cell counts and protein content then fall abruptly until towards the end of the first week, when a second rise takes place. During the first phase of the reaction most of the cells are polymorphonuclear leucocytes; during the second phase they are virtually all lymphocytes. The first phase is accompanied by a sharp rise in the bromide ratio, to the order of unity, and this rise usually continues to increase until the second phase of the reaction is beginning to subside. Even then it may be many weeks before the barrier is fully restored.

One of the reasons why bromide has proved such a useful tool in studies of this kind is that it is excreted so slowly that there is ample time for equilibrium to take place between blood and C.S.F., while in these concentrations the ratio is independent of the absolute amounts of bromide present (Hunter *et al.*, 1954; Fig. 1).

In summary then, the intrathecal tuberculin reaction exerts a dramatic effect on the blood-C.S.F. barrier to bromide; but while the permeability of the barrier increases most rapidly during the first phase of the reaction, the maximal increase in permeability is delayed until the second phase has developed.

The penetration of penicillin.—The effect of the reaction on penicillin is rather different, in that the increase in penetration during the first phase of the reaction is often negligible while during the second phase a considerable increase in penetration takes place. Indeed, the increase in the penicillin content of the C.S.F. appears to be dependent on the second phase of the reaction; and in anomalous reactions, where the lymphocytic phase did not develop, the C.S.F. was never found to contain more than a trace of penicillin, even though thousands of polymorphs might appear during the first phase of the reaction, with a sharp increase in the permeability to bromide.

It appears, then, that intrathecal tuberculin exerts a specific effect on the blood-C.S.F. barrier; nor have we been able to find any record of a comparable effect with any other

factor. This appears the more significant as the amounts of tuberculin given are probably of the same order as those present in tuberculous meningitis.

The effect of cortisone.—The effect of intrathecal tuberculin appears to be antagonized by cortisone. Thus in one case 2 reactions were produced at different times to the same dose of P.P.D. in the same subject. Before the second reaction 50 mg. cortisone was given by mouth the same morning as the P.P.D. The polymorphonuclear component failed to develop though the second phase of the reaction was unaffected. Even under the influence of this single small dose of cortisone the barrier was less affected than in the unmodified reaction and was restored more rapidly (Smith *et al.*, 1957; Fig. 4).

Conclusions.—These findings go some way towards explaining the divergence of opinion that still persists as to the necessity or otherwise of giving penicillin and streptomycin by intrathecal injection in the treatment of meningitis. To take the question of penicillin first: As the results obtained in the intrathecal tuberculin reaction show, the penetration of penicillin into the C.S.F. does not run parallel with the intensity of the inflammation as measured by height of the pleocytosis and the protein content of the C.S.F. In fact, during the first or polymorphonuclear phase of the reaction, when the C.S.F. is often indistinguishable from that in a case of purulent meningitis, little or no penicillin may be found in the C.S.F. This is in line with our clinical experience, that the passage of penicillin from blood to C.S.F. is far too erratic to be depended upon in the treatment of such a serious disease as purulent meningitis. For example, though it is often claimed that pneumococcal meningitis can be adequately treated by intramuscular penicillin, we have failed to detect more than a trace of penicillin in the C.S.F. of a child of 7 months, weighing 7·7 kg., who was suffering from pneumococcal meningitis and who was receiving 5,000,000 units of penicillin by intramuscular injection every two hours (Smith, 1951). Moreover, reports of sizable series of unselected cases of pneumococcal meningitis in which the mortality has been reduced to the order of 10%, have, so far as I know, still only come from centres where intrathecal medication is given.

The position with regard to streptomycin is rather different. In untreated tuberculous meningitis we have frequently found from 5–15 units per c.mm. in the C.S.F. six hours after the intramuscular injection of a gram of streptomycin. This is well above the *in vitro* bacteriostatic level for virulent human bacilli. Yet it has been conclusively shown that the results obtained in the treatment of tuberculous meningitis with streptomycin alone are significantly better when both intrathecal and intramuscular injections are given than when the systemic route is used alone (Medical Research Council, 1948). It therefore seems logical to ascribe the improved results to the very high concentrations in the C.S.F. that persist for some hours after an intrathecal injection.

It is often said that the advent of I.N.A.H. has made the intrathecal administration of streptomycin unnecessary. Though this is not the time to discuss the merits of systemic treatment alone versus combined systemic and intrathecal medication (Smith *et al.*, 1956), it is perhaps worth saying that at Oxford, where combined treatment is still given, we have seldom been kept so busy with requests from elsewhere to take patients whose response to treatment has been disappointing as during the last year to eighteen months. It is tempting to relate this increased demand for our services to the growing tendency to dispense with intrathecal therapy.

It has now been shown that the increase in barrier permeability caused by meningitis varies both with regard to different substances and with regard to the ætiology of the infection. Before, therefore, any one drug can be accounted effective in the treatment of any case of meningitis, it must be shown that, in that particular infection that particular drug is capable of crossing the blood-C.S.F. barrier in therapeutic amounts. It must also be remembered that if cortisone is used in treatment the effect may well be to restore the barrier at the very time when maximal penetration of the drug is most urgently required.

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United Services Section

President—Sir CECIL WAKELEY, Bt., K.B.E., C.B., F.R.C.S.

[*June* 6, 1957]

DISCUSSION ON THE MANAGEMENT OF MASS CASUALTY SITUATIONS IN TIME OF WAR

Lieutenant-General Sir Alexander Drummond (Director-General, Army Medical Services):

INTRODUCTION

The Organization of the Medical Services of the Army for Mass Casualties

The prime objective of the Army in planning methods of handling and treating mass casualties is to find ways and means of maintaining the standard of treatment it is accustomed to give to the individual patient. The fewer the casualties requiring professional, as opposed to lay skill, the easier it is to maintain this standard. Preventive measures are therefore the first essential. All ranks or, colloquially speaking, the man in the street, must have knowledge of and be skilled in the practice of first aid to an hitherto unparalleled degree. Following a nuclear incident or a series of nuclear incidents there will be no time to think or read somebody else's experience, neither will there be scope for professional individualism in the treatment of the injuries. Some surgeons had to learn this lesson again after the landing in Port Said.

The principles of military as distinct from routine civilian surgery have grown out of bitter experience and must, if our patients are not to suffer, remain inviolate. The experienced forward surgeon knows well that his role is the preparation of wounds for delayed primary suture in five to seven days' time, the stepping stones to which are efficient debridement and the firm support of traumatized muscles in the same manner as fractures are cared for. If these principles are adhered to the formation of scar tissue is minimized, compound fractures are converted into simple ones and the patient's limbs and life are not jeopardized. To ensure this standard of treatment the more experienced surgeons must be posted to forward units to supervise those with less skill.

The medical and nursing personnel at hospitals and field units must be protected from being swamped by an influx of minor casualties or unsuitable operative risks. They must also be organized in order to prevent fatigue and overwork. For example, if surgical teams have to sustain their effort and work unremittingly for seven to nine days they can only undertake 12 serious cases per day, no more. Again, to obtain the maximum effort the staff must be provided with a suitable environment in which to work and rest, as in times of stress they must not be worried and annoyed by administrative detail.

As practised in the Great War and World War II, casualties in the forward area should be separated into those who now can be efficiently taken care of by nursing orderlies, the transportable risk cases and those who are seriously or dangerously ill. It is only this last group that should concern the receiving hospitals. Having been diagnosed by an experienced clinician, there will be no need for the patient to go through the routine of the reception or the casualty department at the receiving hospital, a procedure which in these circumstances is a waste of time and medical man-power. The Army practice is for convoys of 5–6 ambulance cars to be sent to a particular hospital or receiving unit. Admission is then direct to the ward. Here the patients are taken over by the nursing and documentary staff and bedded down. If suffering from burns or abdominal injuries intravenous drips and, where necessary, gastric suction are started immediately. Sedation and antibiotics are given as required. In 60 minutes 100 patients can be comfortably settled in bed or on stretchers, having been placed on sustaining treatment, and be waiting for the medical officer to do his round and re-assess their condition. The aim is that the ward will be as quiet and as peaceful as, say, the wards of your hospital on a Sunday morning. If extra skill such as surgical teams is not available, those at the receiving unit must be prepared to sustain and care for their patients for the first few days. The difficult period is the first three or four days; after this pressure should lessen. The likelihood of having settled blood available in the first few days is not strong.

The problem of casualties occurring in enormous numbers is an important administrative one, which has in two World Wars been successfully handled. There is no reason why it should not be so in any future war. The surgeon and physician problem is that all casualties cannot be dealt with in the first six or even ninety-six hours. However, with careful selection and sustaining treatment there is little reason to doubt that at the end of seven to nine days the vast majority of patients will have been successfully treated.

Administratively an important question is to determine beforehand how many beds for seriously ill patients hospitals can maintain. This figure is the limiting factor. I feel that the crisis expansion cliché is a snare and delusion. The conception of beds placed cheek by jowl with patients on stretchers underneath them is fraught with danger. If a hospital has 400 beds, can its staff, which in all probability will be depleted, adequately look after 400 seriously or dangerously ill patients? Is it right to ask them to expand by 50% or even 15%? Experience shows that crisis expansions are possible only if a goodly proportion of the patients are suffering from skin disease, ingrowing toe nails or dyspepsia.

Having determined the critical figure—that is the number of seriously ill patients the hospital can look after, not merely accommodate—that number and that number only should be admitted. The hospital gates should then be locked. Otherwise instead of doing the most good for the greatest number one will do a great number a disservice. If, however, you can augment the staff by putting in a medical company consisting of say 3 medical officers, 6 State-registered nurses, 3 cooks, plus 37 nursing orderlies, the hospital will be able to accept a further 100 seriously or dangerously ill patients.

To-day a medical company whose establishment is 49 is expected to have a 100-bedded-tented hospital erected, opened up and with the majority of its patients admitted and on sustaining treatment within two hours of arriving on site. Field ambulances or casualty filtering units operating within a specified sector will give the rearward hospitals breathing space in which to orientate their organizations.

In the Army we are emphasizing forward surgery. We believe that where possible mobile hospitals should move right into the devastated area to deal with the desperately injured.

Colonel T. M. R. Ahern: *Sorting, Early Treatment and Evacuation*

The city we are about to consider is in Britain and has one million inhabitants. A 10-megaton (hydrogen) bomb has fallen on its centre. Houses are destroyed or damaged and streets blocked by debris for a radius of fifteen miles. There are 210,000 immediate casualties excluding the dead. Of these, 60,000 are light cases and 150,000 are seriously hurt. Of the latter, 100,000 are trapped and some will be released, dead or alive, to-day and over the next few days. There are 50,000 untrapped serious casualties, to be evacuated to hospitals as soon as possible. This is the debit side of the ledger. On the credit side there are over 50,000 hospital beds at distances of from 5 to 15 miles from the edge of the devastated area—just enough to care for the untrapped serious cases, but not enough for the trapped cases who will follow. The majority of these beds are, by current civil defence planning, more accurately, stretchers or mattresses on the floors of schools or churches.

This represents almost the worst possible civil defence situation. There is here a greater disproportion between the medical task and available medical means than is likely to be faced by the armed forces in the field. If we can plan for this situation, the plan can be adapted to any lesser task in the field.

What really happens when a sudden disaster, even a much smaller disaster, hits a community?

There are many well-documented accounts of disasters which caused large numbers of casualties—tornados in the United States of America, bombing of this country, the famous fire storm at Hamburg in 1944, the first atom bomb at Hiroshima. In all these disasters, medical men, among many others, tended to be overwhelmed by the size of the problem and to act irrationally. Casualties suffered because there was no clear-cut plan for the disposal and treatment of large numbers of injured. The case of Dr. Sasaki at Hiroshima is not un-typical. He was working in a hospital, trying to deal with crowds of wounded soon after the nuclear explosion. The account states: "Tugged here and there in his stockinged feet, staggered by numbers, bewildered by so much raw flesh, Dr. Sasaki lost all sense of profession and stopped working as a skilful surgeon and sympathetic man: he became an automaton, mechanically wiping, daubing, winding, wiping, daubing, winding."

It becomes clear that a system of casualty sorting is needed, to be applied well forward of the hospitals, to the whole accessible periphery of the nuclear explosion. Sorting is the process of dividing the injured into categories, so that they can be properly routed either for early emergency treatment or on to medical installations appropriately situated and equipped for their care. This is not a new idea. The method was widely employed during the last war, and is needed whenever there are more injured than can be immediately attended by the available medical force. The criteria for sorting will vary according to the number of patients awaiting medical care and the available medical facilities: the sorting criteria used by the Royal Army Medical Corps in the 1939–45 war would not apply to this situation.

Study of the effects of nuclear weapons suggests the categories for medical sorting which would best permit the largest possible number to receive adequate medical care:

Minor treatment.—Those who, after first-aid treatment, can care for themselves, at least for a few days—40%.

Immediate treatment.—Candidates for immediate life-saving surgery or transportation. Hæmorrhages from an easily accessible site, cases needing tracheostomy, incomplete amputations—20%.

Delayed treatment.—Those with non-critical injuries who can await treatment until they reach hospitals farther back—20%.

Expectant treatment.—Patients with critical injuries, for whom appropriate treatment is unlikely to be available; who are unlikely to survive evacuation or to benefit by treatment—20%.

Starting from these sorting categories, and the rough forecast of the proportions in which they are likely to occur, it becomes possible to plan an appropriate "filter unit" to meet the requirements. I suggest that there may be a critical size for such a unit, above which it becomes wasteful of medical personnel and below which it becomes incapable of full economic function. The total complement, nearly 300 persons, of a unit which might be expected to deal with some 6,000 casualties in twenty-four hours may appear large, but nearly half this total comprises unskilled stretcher bearers, who may, in the event, be provided by local inhabitants.

The present thought on the filter unit is that it should comprise some 10 doctors, 120 nurses and nursing auxiliaries and 160 non-skilled people to act as stretcher bearers, police, &c. In military equivalent this corresponds roughly to the present Royal Army Medical Corps field ambulance to which is added a company of infantry for stretcher-bearer and police work.

The filter unit is designed (Fig. 1): (1) to monitor and, if necessary, to de-contaminate the wounded (of radio-active dust or material);

Diagrammatic layout of a filter unit.

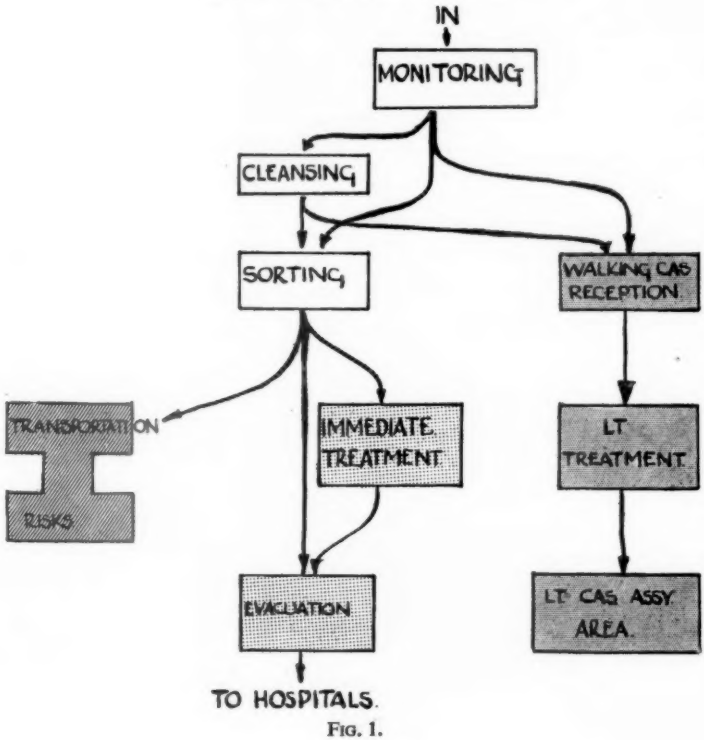


FIG. 1.

(2) to separate the lightly from the seriously wounded. This is a rough sorting procedure which separates the first category from the other two. The test here is to establish whether a man can walk, and, if so, whether he can fend for himself for a few days. If he can do this, he is a light case. After first-aid treatment, he is sent on to the welfare section of the Civil Defence organization and out of medical ken and carriage;

(3) to pass all other than light cases through the sorting department. An experienced surgeon works here over-seeing the work perhaps of other doctors. This is the heart of the filter unit. The injured will be sorted into categories. First, those who will be saved by simple immediate surgery, and who, lacking this, will quickly die. These will be sent direct to the immediate treatment department. Second, those whose condition allows them to wait for surgery. They go direct to the evacuation department, and so on to the hospitals farther back. Thirdly, the "transportation risk" cases who should be held in a hospital specially set aside for this purpose. These are the grimmest results of the sorting process. They have not much chance of survival, and their disposal will be discussed later.

Is it a waste of surgical skill to employ the best and most experienced surgeon here as a referee, rather than working in his operating theatre? Which scale is more heavily weighted—the one holding the fifteen or so cases he might have operated upon in the first thirty-six hours, or that holding the three or four thousand he may have placed in their correct categories in this time? Is surgical experience so important at this point? Decisions on sorting, which are literally of vital importance, will have to be made rapidly, without diagnostic aids and relying wholly on clinical acumen. All must depend on the ability and experience of the individual who has responsibility for making these decisions.

The "immediate treatment department" is for those whose injuries will soon prove fatal unless some simple surgical procedure—ligature of an artery, tracheostomy, completion

Filter unit. Breakdown of 6,000 casualties in twenty-four hours.

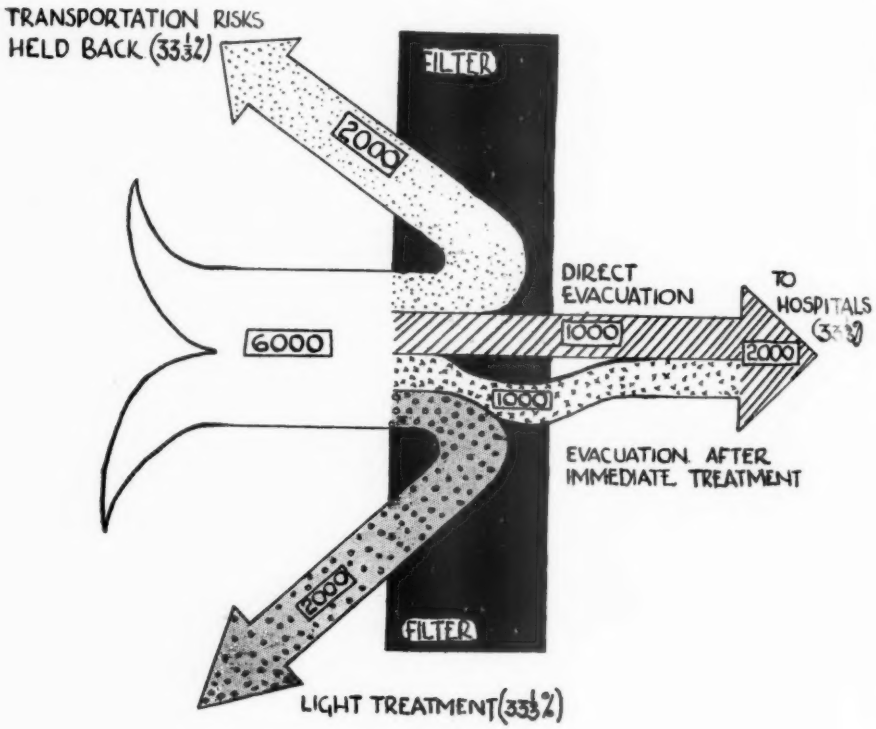


FIG. 2.

of a partial amputation—is quickly performed, but who will then be able to wait for more thorough treatment. It aims to convert bad surgical risks to good ones. If it is to do this successfully there must be team work of a high order, and medical auxiliaries must perform many tasks and accept responsibilities well beyond those normally required of them. New training directives will provide for the training of every army medical service other rank in such procedures as injections, intravenous infusions, catheterization, taking blood pressure, and to assist at such advanced procedures as burns care, tracheostomy, aspiration of the pleural cavities, lumbar puncture and plaster of Paris technique. Men (or women) trained in this way, and trained to work as teams, could adequately staff this immediate treatment department.

The "evacuation department" is a convenient place to hold casualties who are bound for the rearward hospitals, until transport becomes available. It will manage the loading of ambulances in an orderly and economical manner, and make sure that those cases given a high priority by the sorting surgeon go on first.

A "holding department", to hold 100 transportation risk cases, has been incorporated with the filter unit. There are all sorts of reasons why these unfortunates should not be sent farther back than necessary, but, initially, there will be no near-by installation ready for them. Until a special hospital can be set up near-by it will be best to provide facilities on the spot to care for some of them. The great majority of these patients will have little or no hope of survival. No drugs may be available for them except perhaps sedatives or narcotics. There may not be nearly enough transfusion fluid, or surgical or nursing time and effort, even for those who may be expected to recover. It would be unrealistic to expend them on such as these: but it would be indefensible to abandon them. If their condition improves, their category will be re-assessed. As a personal opinion, a small part of the all too scarce medical effort should be devoted to their comfort for the four or five days most of them can expect to live.

Lastly, there is the non-skilled labour, without which the filter unit could not function. Policing is likely to be a real necessity. The filter unit will be invaded by people searching for missing relatives. Its store of food and drinking water will attract those who are without these things. It could easily be overrun unless drastic plans are made to prevent this from happening. Then, there is the stretcher-bearing problem. Remember that some 4,000 stretchers are to be carried through the departments, and then loaded into transport each twenty-four hours. This entails a major labouring effort for at least 100 men.

I am going to suggest to you that hospital arrangements farther back may be competent or chaotic accordingly as casualty sorting at this vital level succeeds or fails. Sorting is the key to effective management of large numbers of casualties.

If the filter unit sorts and treats 6,000 casualties in twenty-four hours successfully it will have achieved the following (Fig. 2):

(*a*) Treated and cleansed the light cases (33·3% of the total) and then diverted these to non-medical welfare channels.

(*b*) Separated the non-transportable cases from the rest.

(*c*) Given emergency life-saving surgery to over 1,000 persons, who should now survive and will be evacuated to acute hospitals—and who would not otherwise have survived to reach these hospitals.

(*d*) Arranged the evacuation of those other serious casualties who do not require immediate treatment at this level.

(*e*) In all, diverted about two-thirds of the casualties (i.e. the light cases and the non-transportables) from the use of medical transport and the doors of the hospitals.

The problem here has been to make available a minimum useful standard of professional treatment to the greatest possible number but to be sure the standard does not fall below this minimum. Remember that there may be at least 6,000 waiting for each 6,000 treated. The surgeons have, on an average, two minutes to categorize each case. Responsible surgical opinion says this is feasible in the circumstances. The treatment teams here can afford an average of nine minutes for each emergency surgical case. Are they going to be able to do real good in this short time? Thank God we none of us have experience. The guess I give you is that they can.

Finally, here is an extract from the report on the Worcester (Massachusetts) incident of 1953. The author is summing up his findings, and the report reads:

"There is an attitude among doctors and administrators in civilian hospitals which opposes the suggestion that assignment of patients should be made by any central authority. This over-confidence in the independence of one's own hospital varies in its expression from extreme belligerence to a guarded willingness to consider the recommendations of central authority. It was present among most of the physicians and administrators encountered in this survey, and it must be reckoned as an attitude of mind which will need consideration in future planning."

Lieutenant-Colonel R. E. Waterston: *Treatment of Fractures of the Extremities*

It is essential that we have a plan for the management of the less severely injured, as well as for the serious cases. In the next few minutes I am going to put forward a scheme for dealing with some of the fractures—fractures of the upper limb, and of the lower limb below the knee. These are cases which would normally be treated in the out-patient departments of our hospitals. What we want is a standardized scheme of treatment which fulfils the following three criteria:

(1) that there is the least possible demand on doctors;

(2) that the patient can return home or to a welfare centre and not be dependent upon a hospital bed;

(3) that it is safe and requires a minimum of attention for four to five days when the patient can have his final definitive treatment.

It will be universally agreed that for fractures some form of splintage will be necessary, but standard first-aid methods vary enormously and largely depend on improvised splints and most of them do not fulfil the criteria we demand. Our Director-General, Lieutenant-General Sir Alexander Drummond, suggested the use of plaster of Paris for this purpose, and working on this idea a standardized technique of six basic "P.O.P. splints" has been worked out.

At the "filter unit" cases requiring this treatment are selected by the responsible doctor examining the cases, each is labelled according to his injury and the case passed to the team of orderlies who apply the plaster.

The basis of this whole method of treatment is the use of plaster of Paris in the form of *slabs* or *gutters*—these are applied in the long axis of the limb and are fixed by an open-wove cotton bandage, which is cut when the plaster has set. An essential feature is that in no instance is a limb actually encircled by plaster.

The chief advantage of plaster over other splints is, of course, that it moulds to the contour of the body, and can therefore be applied directly to the body surface without risk of pressure. There is no reason why a slab should not be applied over a silk stocking, a shirt sleeve or a sock, but not over a trouser leg or a jacket sleeve and not over a shoe.

The splints shown in Fig. 1 are, of course, intended for the treatment of simple fractures but the method is also applicable to the treatment of compound fractures with the proviso that the patient would have to remain under close medical care. Also, and most important,

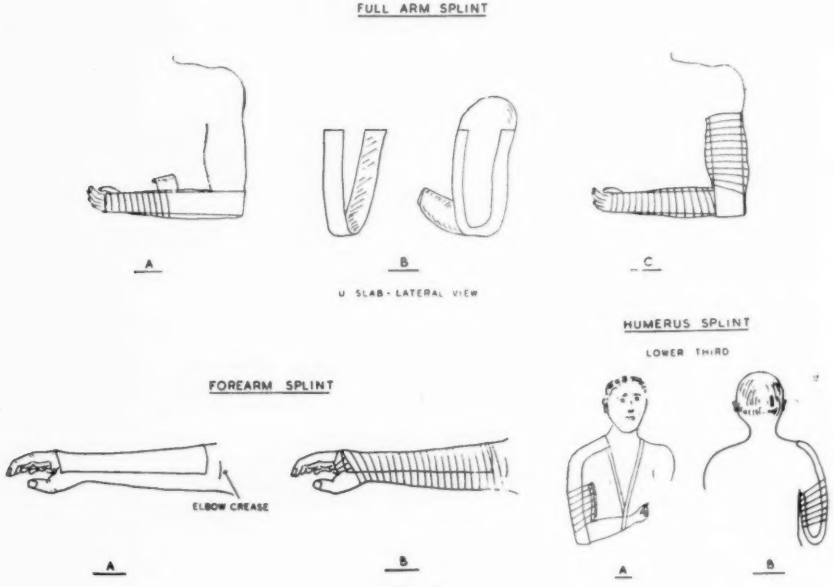


FIG. 1.

the slab would have to be applied over a dressing and when the plaster had set the cotton bandage would be cut all the way up. Our orderlies who are taught to apply these plasters work in teams of two, one to apply the plasters assisted by the second who supports the limb. They are taught to instruct patients to elevate the limb afterwards to avoid reactionary swelling.

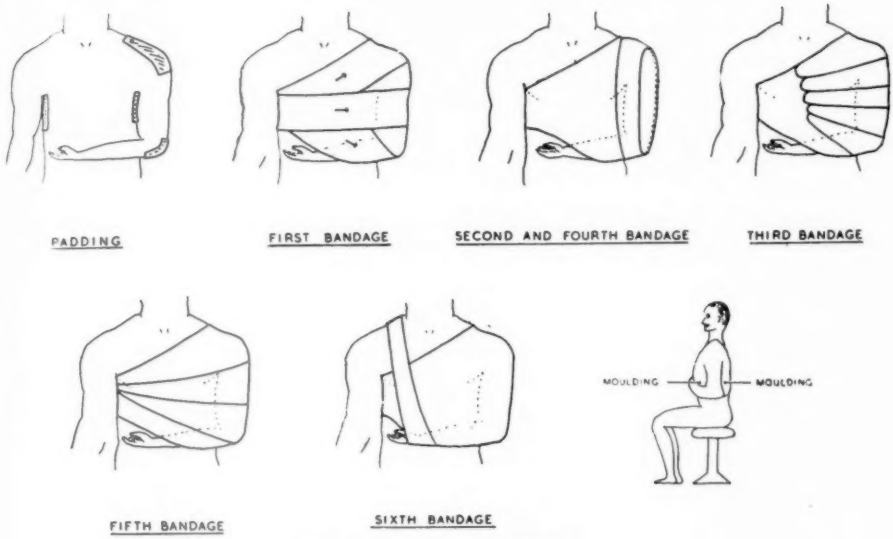


FIG. 2.—Thoraco-brachial splint.

The next "P.O.P." is the thoraco-brachial plaster (Fig. 2). This splint is included in the series because in the last war it proved to be such an invaluable splint for evacuating cases of shoulder injury and fractures of the upper end of the humerus. It is applied with four pads to protect pressure points and though it encircles the chest the arm is not encircled.

Lower limb P.O.P.s.—Fig. 3 demonstrates:

(1) *Below-knee plaster for fractures in ankle region.*

The method for the below-knee P.O.P. is to apply this with the patient prone. With two-men teams this is the simplest method for applying plaster though not of course for maintaining the reduction of the fracture. I should explain that in all these cases we do not expect orderlies to reduce the displacement though they are expected to correct any angular deformity. The patient's final treatment takes place four to five days later under medical care.

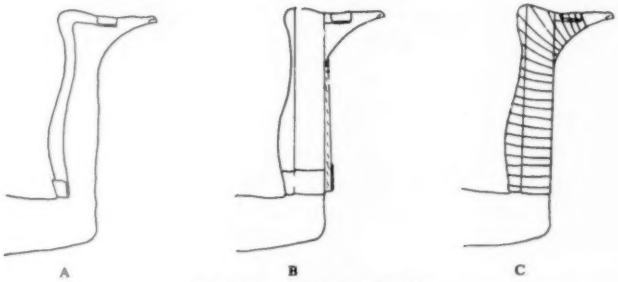


FIG. 3 (1).—Below knee splint.

(2) *Long-limb P.O.P.*—This plaster is intended for fractures of the shaft of the tibia. With some support behind the knee, two long antero-medial and antero-lateral slabs are applied from mid-thigh to foot. These are fixed with an open-wove bandage. The foot is steadied by one orderly while the second does the plastering.



FIG. 3 (2).—Long leg splint.

These methods are applicable to patients being treated at the filter unit, but it may well happen that a patient admitted to hospital with another injury may also have a fracture, in which case a plaster splint could be made in the hospital ward. This is the reason why I include a chest plaster—a simple plaster encircling the thorax—which has been devised in consultation with thoracic surgeons for bilateral rib fractures or floating sternums in which there is paradoxical movement of the chest wall. I am assured that this plaster does help to fix the chest wall and enable the patient to use his diaphragm to the best advantage.

Lieutenant-Colonel R. S. Hunt: *The Treatment of Mass Burns Casualties*

The effects of the Japanese bombs, H-bomb tests, and various civil disasters have been the basis of all planning. However, in the Services let us remember that we may have to face nuclear attack anywhere in the world, on land, on sea, in a city or in a desert. Wherever it may be, the number of casualties will far exceed the available medical aid. The magnitude of the problem is illustrated by the estimate that if a 10-megaton weapon exploded over London, there would be 135,000 cases of burns!

The questions are *what* do we do in the way of treatment, and *how* do we do it?

As far as burns are concerned we must apply the principles adopted in peacetime, modified to suit these particular circumstances. Our main object is "to do our best for the most". Authorities tell us that one-third of the burns will be "minor" cases able to look after themselves and each other, one-third will be "moderate" and will require energetic treatment, and one-third will be so severe as to be "non-transportable"; a better term than "hopeless". It is the middle group that we must concentrate on, 20 to 40% body surface burns, and they will include women and children as well as young people and old. Throughout treatment we must do our utmost to keep their spirits high.

I think it is agreed that the care of the burnt surface is of secondary importance and should be deferred until the general state has been stabilized by adequate fluid replacement. Here we run into difficulties straight away. First, blood will be virtually unobtainable and plasma expanders will have to be used instead. Second, many of the usual sites for intravenous infusions may be burnt and "cut downs" will be needed to introduce plastic tubes. To avoid repeated operations of this sort and to encourage the drip to run for longer it helps to put 10 c.c. of a 1% solution of procaine into the infusion bottle. Fluids must not be given at random but according to physiological needs with a balanced intake and output. In times of stress like this, with a gross shortage of staff, anything that will help us to calculate the volume of fluid required and to measure the output is to be commended. For the first of these the chart shown in Fig. 1 contains much useful information. For the second, it has been suggested that an indwelling catheter draining into a bottle would be a quick way of seeing if the urinary output was adequate.

Penicillin and streptomycin are probably the antibiotics of choice but there may be no choice and any that are available will have to be used instead. Sedatives will be needed too, but here again the choice may be limited.

There is a great difference of opinion about the best way to treat the burnt surface by "exposure" or "dressings". I do not honestly think that in these circumstances there will be any doubt as to which we will have to use. It will be the "exposure" method. Obviously there are exceptions for which the dressings available should be reserved. For example if a case was burnt back and front one surface would have to rely on dressings. Another example is burns of the hands which are best immobilized in the position of function in dressings. Now, in spite of all I have said there is one thing certain in a disaster like this, there is no room for differences of opinion. All cases will have to be treated according to a generally accepted method. To give way to the "man who knows a better way" will cause chaos. It is a waste of time and effort to keep changing treatment.

I cannot leave the heading "*What to do*" without briefly mentioning four urgent procedures.

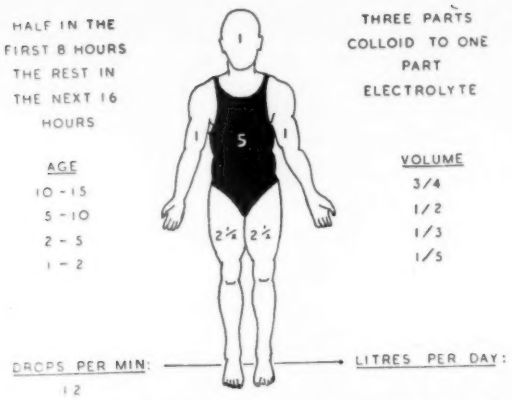


FIG. 1.—The figures on the limbs and body denote the number of standard transfusion bottles of fluid required in the first twenty-four hours.

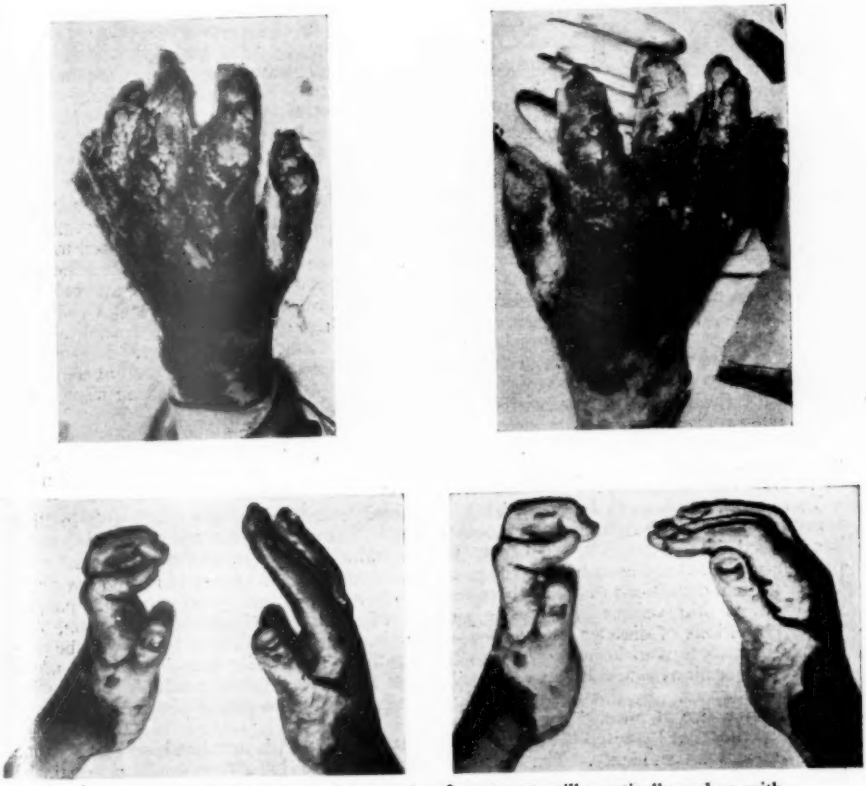


FIG. 2.—Hands, before and after months of treatment, still practically useless, with disorganized, immobile joints.

Tracheotomy for burns of the air passages, tarsorrhaphy to lessen the chances of blindness, and gastric suction for those who develop acute dilatation of the stomach. Last, but not least, amputation. I am sure that amputation in selected cases will convert severe cases to moderate ones or even moderate to mild ones. The obviously pickled hand with thrombosed veins and marbled insensitive skin is better off than allowed to remain and intoxicate the patient in the chance that something useful could be made of it after months of suffering and effort. Fig. 2 is an example of what I mean. The same applies to a completely charred limb.

When thinking of operation it is important to remember that it should be done within the first forty-eight hours if healing by first intent is to take place. After this time the effects of radiation, causing leucopenia, begin and healing is delayed with an increased risk of infection. Do not forget that burns cases may have other injuries as well which require operation before the burn can be treated!

So much for the general principles. Now *how* to carry them out with this vast disproportion between patients and staff? I think there are two main elements in this compound problem, one is *time* and the other *numbers*. We must reduce the *number* of patients and increase the medical man-power! Both can and must be done if the nation is to survive. How?

(i) *By evacuating likely target areas of all but essential workers.—Not* a medical responsibility but a great help.

(ii) *By educating the public in methods of self-protection and self-help.—Partly* a medical responsibility. A part of training which we all tend to forget.

(iii) *By the careful sorting of casualties.*—This is the most important consideration of all for doctors. To be effective it must be done by the most experienced doctor available, as near the scene of the disaster as possible and as soon after it as possible. The choice of category lies between the following, or any combination of them, and it may be very difficult:

Minor burns.
Moderate burns.
Severe burns.
Complicated burns—with other injuries as well.
Partial skin thickness.
Full skin thickness.
In the young and in the old.

As a guiding rule young people would take preference over the old in this fight for survival. No case will be denied treatment simply because the patient has been exposed to radiation.

Minor burns will not be a full medical responsibility. They will be encouraged to look after themselves and each other and here there is a tremendous scope for someone with a little imagination and organizing skill. Imagine a centre on the lines of a "help-yourself" canteen. A man at the door to direct you to the appropriate counter according to whether you had face, hands or body burns. Drugs and dressings on the counter, instead of buns and biscuits, to put on your tray or into a bag that you collected at the door. Instructions instead of price tabs and a drink of "salt and soda bic." instead of paying cash at the desk! Do not be too critical of this rough idea. It is merely food for thought and I suggest a visit to the Business Efficiency Exhibition might give better ideas!

So much for some ways of reducing the patients. Now to increasing the medical man-power, particularly the nursing strength, for the nursing of burn cases is of paramount importance. There are many ways but one is outstanding and time prevents discussion on the others. It is *training*.

Team work is essential, *but* it is virtually impossible to have trained teams able to stick together and be at the right place at the right time. To overcome this our Director-General has decreed that everyone in our Corps shall be trained to carry out a limited number of procedures considered essential for the preservation of life for a period of four or five days. Under normal conditions many of these would only be performed by fully qualified people, for example intravenous infusion, aspiration of pleural cavities, catheterization, &c. Under conditions of disaster it would be justifiable, and indeed essential, that they be performed by people who know *how* to do them without necessarily knowing *why* or *when*. These two questions would be the responsibility of the medical officer available to deal with hundreds of cases. By this means it will always be possible to get a fully trained team of at least some size at once.

I said earlier that I wanted to say something about *time*. This problem is so vast because it all happens so suddenly. The time taken to produce 135,000 cases is concertina'd into a few seconds. *Time* has been lost to us. If when we plan we start by thinking how to make up for lost time we will automatically make time to deal with more cases, and make time for the small staff to do more work, or in other words, we will increase the man-power.

BOOK REVIEWS

Postural Drainage. By E. Winifred Thacker, M.C.S.P. (Pp. viii + 56; illustrated. 8s. 6d.) London: Lloyd-Luke (Medical Books) Ltd. 1956.

This little book by the Superintendent Physiotherapist at Harefield Hospital admirably achieves the objectives of the author which are to illustrate the technique of postural drainage and to demonstrate the important place which expert physiotherapy occupies in the treatment of chest disease. As Mr. T. Holmes Sellors remarks in his Foreword: "This development in the realm of physiotherapy is a special contribution that has been made by British workers . . .", a statement which this book bears out. It is short, it is clearly written, and it is fully illustrated. Miss Thacker has been at pains to lay stress upon the practical details of the subject and she gives many valuable hints in the management of patients which are seldom found in other accounts. This monograph can be confidently recommended to anyone who is interested in this side of chest work.

Functions of Autonomic Transmitters. The Abraham Flexner Lectures, Series Number Thirteen. By J. Harold Burn, M.D. (Pp. ix + 228; illustrated. 40s.) Baltimore: The Williams & Wilkins Co. London: Baillière, Tindall and Cox. 1956.

The Abraham Flexner biennial lectures at Vanderbilt University form a heterogeneous series but all have been given by experts and Professor Burn's contribution keeps up the tradition.

The first lecture of general interest is, appropriately enough, on medical education. Here he makes a plea for the greater use of the preclinical sciences and their exponents in the teaching of clinical medicine in Britain, and in his short review of the development of the medical sciences he comments on the latency of important ideas until the time or the necessary techniques are ready to show them to advantage. The next five chapters, on acetylcholine and the heart, ciliary movement, norepinephrine, common properties of different classes of drugs, and the supersensitivity and subsensitivity of denervated structures, form a unified whole leading us through many of the by-ways of pharmacology in search of a common principle of action. The relation of acetylcholine to the genesis of the heart beat is a subject the author has made peculiarly his own. The pharmacology of ciliary movement is dealt with similarly on the theory that rhythmic activity is maintained by the local production of acetylcholine. Then norepinephrine, the most recent addition to the autonomic transmitters, is studied and contrasted with epinephrine. In the chapter devoted to common properties of drugs an endeavour is made to relate these to common modalities of action. This is followed by a study of the factors involved in the sensitivity of denervated structures and its complexity is made obvious. The last chapter is in some ways out of context, dealing with alcohol and nicotine, but even here the Oxford laboratory has contributed to this type of problem. The lectures are a distillate of the work of an active school of pharmacology in which the author has provided many of the stimuli and it is a delight to see the many strands of information brought together and beginning to show a pattern. Since it cannot be regarded as a systematic treatise there is more place for the discussion of matters still open, thus giving an insight into the trends of present-day physiology and pharmacology and allowing the reader to draw his own conclusions. The style is characteristic and clear and the production of the book excellent.

Physiopathology of the Reticulo-Endothelial System. A Symposium organized by the Council for International Organizations of Medical Sciences. Edited under the direction of B. N. Halpern by B. Benacerraf and J. F. Delafresnaye. (Pp. xii+317; illustrated. 45s.) Oxford: Blackwell Scientific Publications. 1957.

The group of workers brought together for the symposium has been selected with sufficient catholicity for the result of their discussions to give an adequate coverage of the present-day knowledge of the functions of the reticulo-endothelial system in health and disease. The introductory lecture by Vallery-Radot on the development of the ideas on phagocytosis and the reticulo-endothelial system is very interesting. His personal links with many of the more important earlier workers give his descriptions an intriguing liveliness. After a description of the reticulo-histiocyte, the principles of the determination of the shape and size of globular proteins are discussed. Then some of the factors involving physiology of the phagocytic function come under review. The general physiology of phagocytosis and the clearance of particles from the blood stream; the effects of variations in particle size on the rate of clearance; the importance of the rate of blood flow through the main RES organs such as the liver, and the effects of blockage by previous particle injections are next considered. Then the liver and the Kupffer cell and the interrelationship with cholesterol metabolism and the role of the RES in hæmatoclasia and iron metabolism come under

review in relation to the general functions of the spleen. The later papers deal with the involvement of the RES in the response to infections and endotoxins and the mechanisms of hypersensitivity reactions and changes in RES storage capacity. The last main paper contains a general discussion on the cells of the RES in health and disease. The interconnexions of this system in liver, splenic and humoral pathology are well outlined. Each paper has a summary either in English or French. The French editors have produced not only a well-edited symposium but an up-to-date reference work on the subject. The book is well produced and the price reasonable.

The Doctor, His Patient and the Illness. By Michael Balint, M.D. (Pp. x+355. 40s.) London: Pitman Medical Publishing Co. Ltd. 1957.

This book sets out the results of research into the doctor-patient relationship made over a period of two or three years by fourteen general practitioners and a psychiatrist. The general practitioners attended once a week as far as possible. To quote the author:

> The special nature of the research not only required frank disclosure by them of many intimate personal details of their daily work, details which by general tacit consent are hardly ever made public; it also required acceptance of thorough and searching criticism of such details. Anybody reading this book cannot but be impressed by the amount and severity of criticism that was given and taken in good spirit during the research; all irritation, hurt personal feelings, vexation were either disregarded or tolerated to enable the research work to proceed.

Needless to say the author is a psychoanalyst. For the ordinary reader vexations have resulted which, it might be thought, can be neither disregarded nor tolerated. Case histories are set out at length, having been faithfully recorded by a secretary, and nothing has been pruned for fear that hidden motives might determine the selection. The result is an intolerable prolixity. The author arrives at conclusions with which few would disagree and he has explained to us why we do not always go down well with our patients. Thus we are told that to tell a patient with symptoms that he has nothing wrong with him is a bad thing to do since it is clearly incorrect. Surely simple propositions of this kind are now accepted even in the teaching hospitals of whose deficiencies the author seems to be so aware.

Even if the reader is left wondering whether his journey through the book has been really necessary, there can be no doubt of the sincerity and conviction with which it has been written.

Rheumatic Diseases, Rheumatism and Arthritis. By Heinrich Brugsch, M.D., F.A.C.P. (Pp. xiv+330; illustrated. 80s.) Philadelphia and Montreal: J. B. Lippincott Co. London: Pitman Medical Publishing Co. Ltd. 1957.

This book is not intended to be a textbook, but an introduction to the subject of the rheumatic diseases. It does not, therefore, suffer from the usual defect of larger books on the subject, namely the obscuring of practical advice by an abundance of theorization, and reports of purely negative research. In spite of the rather tiresome title, the book gives a succinct and largely accurate account of the practical handling of those painful disorders of locomotion for which no satisfactory group title has yet been found.

In format the book closely follows the larger textbooks on the subject, the clinical theme being developed through chapters on statistics, anatomy and physiology, clinical examination and laboratory procedures. In addition to chapters on the chronic articular rheumatic diseases, there are chapters on the diffuse collagen diseases, and on infective arthritis. It is somewhat surprising to find Sjögren's syndrome included in the latter. It is also somewhat confusing that the last chapter is entitled "Diseases Simulating Rheumatic Diseases", whereas the first section of this chapter is devoted to "Nonarticular Rheumatism". The information given is up to date, lucid and practical, though certain surprises await the British reader. For instance, we are told that the term "atrophic arthritis" is preferred in Great Britain; that cinchophen should be used in chronic gout; and that a diagnosis of pleurodynia is acceptable in the presence of a pleural effusion. These defects, however, are few though the excellence of the text is somewhat marred by the poor quality of some of the illustrations.

This is a book which can be thoroughly recommended to the senior student, and as initial reading for the post-graduate student. The latter may well take advantage of the extensive bibliography which appears at the end of each chapter.

Surgery of the Anus, Anal Canal and Rectum. By E. S. R. Hughes, M.D.Melbourne, M.S.Melbourne, F.R.C.S.England, F.R.A.C.S. (Pp. xi+304; illustrated. 50s.) Edinburgh and London: E. & S. Livingstone Ltd. 1957.

In this book the author describes theory and practice in the surgery of the anus, anal canal and rectum which he has found to be adequate; he has not sought to write a reference book. His training in this speciality and present opportunities to practise it have fitted him to achieve his objective. The general classification of the subject-matter follows the accepted helpful

pattern; the early chapters deal with surgical anatomy, symptoms and investigations. In the former chapter the extent of the rectum is defined as from the recto-sigmoid junction to the ano-rectal ring but the author states it is difficult to define the position of the junction with the sigmoid. This is an important point in deciding whether an anterior resection of the rectum should be done for carcinoma. The author points out that anatomists place the junction opposite the third piece of the sacrum; at this point the sigmoid mesentery ends and it is about 15 cm. from the anal orifice on sigmoidoscopy. The treatment of ano-rectal surgical wounds is of practical interest and the author describes the advantages of primary suture and primary free skin grafting. After excising a large fistula the control of hæmorrhage may not be adequate for immediate skin grafting and a delayed primary skin graft is advocated. Technical difficulties encountered with the latter are outweighed by the advantages obtained by the patient.

It is gratifying to read in the post-operative treatment of hæmorrhoids that the rectal tube has no particular value and that the bowels can act when the urge arises within twenty-four to thirty-six hours after operation. The author deals with carcinoma of the rectum in a full and practical manner—the standard operation is the abdomino-perineal excision of Miles and the synchronous combined method is well described. Regarding the perineal dissection the author rightly states that the posterior end of the wound heals better if it deviates to one side of the mid-line out of the natal cleft and a wide area of skin need not be excised. But is it always necessary, or advisable, to excise the coccyx? If the carcinoma invades the vagina it should be stressed that a Wertheim's hysterectomy should be combined with the Miles' procedure.

The author regards the anterior resection of the rectum as the procedure of choice for tumours in the upper third of the rectum. It must be clearly stated that patients for the operation must be selected carefully and a meticulous operative technique employed to minimize the risk of recurrence. The historical appendix forms a fitting ending to a book which is well written, replete with illustrations clear and valuable, and full of practical instruction for those who are engaged in this speciality. This book is a most helpful addition to the literature of the subject and is strongly recommended.

Operative Surgery. Editors: Charles Rob, M.C., M.Chir., F.R.C.S., and Rodney Smith, M.S., F.R.C.S. In 8 volumes and index. (Volume 4 Head and Neck and Clearance of Lymph Nodes. Vascular Surgery. Endocrine Glands: illustrated. £5 10s.) London: Butterworth & Co. (Publishers) Ltd. 1957.

With the appearance of the fourth volume, the half-way point has been reached, and one can begin to form a judgment on the work as a whole. The favourable impression created by the earlier volumes is confirmed, and it now seems unlikely that the subsequent volumes will alter this verdict. The subjects now dealt with are the head and neck, clearance of lymph nodes, vascular surgery, and the endocrine glands. Only minor procedures are dealt with in the Head section, and presumably major procedures will be considered in a subsequent volume. This section illustrates the difficulties of selection confronting the editors of a work such as this, but it is questionable whether excision of a sebaceous cyst of the scalp merits inclusion. Since it has been included, it is a pity that the author has rejected the very simple and efficient procedure of transfixion-enucleation. Throughout the Neck section, the importance of cosmetic skin crease incisions is rightly stressed, but in some chapters might have been more stressed. There are very few neck operations in which long skin crease incisions, if necessary multiple, cannot be made to give perfect access. In this section, Raven's chapters on carcinoma of the pharynx and Ewing's on block dissection of the neck may be specially mentioned. In the chapter on excision of axillary lymph nodes, one is surprised to see the fallacy still persisting that excision of the sternal part of the pectoralis major is necessary for adequate exposure of the axilla. There are good accounts of the various operations for carcinoma in the region of the oral cavity, but in the chapters on carcinoma of the tongue and lip, there is no mention of any other treatment but surgery. If radiotherapy is to be completely ignored, why have a paragraph on indications at all? In the section on the salivary glands, if Pattinson's advice on the technique of sialography is followed, the damage so often caused by this procedure in the parotid gland will be avoided. There is a description of parotidectomy with conservation of the facial nerve modified from the technique of Redon, who in France during the last war was responsible for the establishment of the operation as a standard procedure. Up till now, detailed accounts of this operation in the English literature have been both rare and difficult of access. In the operation of removal of the submaxillary gland, the importance is emphasized of Hayes Martin's manœuvre of identifying the cervical branch of the facial nerve as it crosses the facial vessels and before these vessels are secured. It is surprising how many surgeons still do not realize that by omitting this simple little anatomical exercise during removal of the submaxillary gland they

are condemning 50% of their patients to a permanent wry mouth. In the Vascular section, Cockett's article on ligation of the ankle perforating veins, and Eastcott's on exposure of and grafting operations on arteries are worthy of special mention, as well as Mowlem's straightforward account of excision of subcutaneous tissues for lymphedema, in which once classical procedures which have failed to stand the test of time are mercifully not mentioned. In the section on the Endocrine Glands, it is interesting to note that the author has come down on the side of routine identification of the recurrent laryngeal nerve during thyroidectomy. The inclusion of a chapter on interstitial irradiation of the pituitary, however, is premature. In the section on operations on the adrenal glands, the lumbar, abdominal, and transdiaphragmatic routes are all described. Space will not allow of further detailed criticism, but enough has been written to indicate why this volume has created a favourable impression in spite of some minor weaknesses.

Modern Trends in Geriatrics. Edited by William Hobson, B.Sc., M.D., D.P.H. (Pp. vii + 422; illustrated. 72s. 6d.) London: Butterworth & Co. (Publishers), Ltd. 1956.

"Modern Trends in Geriatrics" is an excellent textbook on the subject and although it is obviously intended mainly for medical personnel many others working in a therapeutic team will find much of interest to study in this work.

It is clear that Professor Hobson has a deep interest in and a wide grasp of the subject and of its importance in the field of Medicine.

In editing this work and writing two sections himself he has made a valuable contribution and as the remaining sections have also each been written by experts a high standard has been maintained throughout the book.

For many the first chapter on "General Problems of Ageing" will prove a most interesting introduction, as it includes a short historical survey and refers to Demographic Changes, Social Pathology of Old Age, The Growth of Social Services for the Aged and Prevention of Disease and Disability in the Elderly. This section contains much useful information, reflects a sound philosophy on the subject and offers sound advice.

Next follow several fascinating chapters on "Ageing from a Biological and Cellular point of View" by Bourne. "Normal Values and the Interpretation of Biochemical Data in the Elderly" by Jordan and "Psychological Aspects of Ageing" by Welford. These sections bring to the clinician results of research and thus explain some results and reactions found amongst the elderly not hitherto fully understood.

These chapters are followed by subjects more familiar to the clinician including "Arteriosclerosis and Hypertension", "Glycosuria and its Significance", "Chronic Bronchitis in the Elderly", "Skin Conditions in the Elderly", "Gynæcology in Senescence and Senility", and "Orthopædic Surgery in the Elderly". Each chapter deals with the subject in a modern and scientific yet practical way and discusses problems which are of considerable importance to those working in the respective fields of Medicine.

The chapters on "Therapeutics in the Elderly" and "Nutritional Problems of the Elderly" each cover a large subject briefly in such a way as to be equally instructive to the student and to the graduate.

Among the final chapters "Hospital Care of the Elderly" by Morton is useful in summarizing the role and general principles of a geriatric unit which have now been in operation in the earlier-established units for about fifteen to twenty years, and which may therefore be used as a safe pattern on which to build for the future.

It is very appropriate that the last two chapters deal with "Problems in the Home Care of the Elderly" and "Employment, Retirement and Health", for no study of Geriatrics could be considered as complete without consideration of these aspects.

The whole textbook is well illustrated with diagrams, graphs, figures and photographs and has a good index.

This is a book which should be read widely and studied by practitioners and consultants working in all fields of Medicine and should find a place in all hospital libraries.

The subject, an important one, is presented well with interest, factual data, the results of modern research and with sound practical advice based on experience.

"Modern Trends in Geriatrics" is treated essentially from a medical point of view, but sufficient reference is made to the social impacts upon old age and ways in which these can be treated to make it more useful and more practical than the average textbook of medicine.

The problems of the elderly sick and the role of Geriatric Medicine in the health of the population is known to many, but how much can be done to prevent disease and to alleviate, in a scientific way, the ills and disabilities of the old is still only partially appreciated and Professor Hobson has done well to introduce the subject for study in an academic atmosphere.

Clinical Electrocardiography. Interpretation on a Physiological Basis. By Manuel Gardberg, M.D. (Pp. xi + 315; illustrated; 95s.) London: Cassell & Co. Ltd. 1957.

There has been a recent spate of works dealing with clinical electrocardiography; this book adds to the flood. It purports to interpret the cardiogram on a physiological basis, and rightly emphasizes the influence of the heart's position on the tracing both in healthy subjects and in patients with heart disease. None the less, no advantage is taken of the valuable procedure of partially correcting the heart's unusual lie in relation to a high diaphragm by recording the tracing from a lead connected with the left leg during deep inspiration.

The author's zeal for explaining every departure of the cardiogram from the normal by reference to the electromotive forces, has meant the introduction of numerous complicated line diagrams whose reading is exceptionally laborious. The quality of the electrocardiograms is often indifferent, and the tracings are frequently artificially improved, while the obsolete lead CF_4 is sometimes shown.

The order in which the various cardiographic changes are described is haphazard. Thus, left and right ventricular preponderance are dealt with in chapters separated by three others. Again, injury to the heart, instanced by cardiac infarction, is separated from a description of coronary disease by four chapters, and of ischæmia by three. Many conditions like hypertension, syphilitic heart disease, mitral and aortic valve disease, congenital cardiovascular disease, pericarditis and anæmia, get scant attention.

To those who appreciate a physiological exposition of the changes in the electrocardiogram in diseased states, this book may give satisfaction, but it is not recommended as a comprehensive work on electrocardiography as applied to the elucidation of the condition of the heart affected by diverse diseases.

Vitamin A. By Thomas Moore, Sc.D.Cantab., D.Sc.Belfast. (Pp. xx + 645; illustrated. 76s.) Amsterdam, London, New York, Princeton: Elsevier Publishing Co. London: Cleaver-Hume Press Ltd. 1957.

In this substantial monograph, the author has presented a broad and detailed survey of present knowledge of the biochemistry of vitamin A and its place in the metabolism of man and animals. It may be stated at once that the whole treatment is scholarly and authoritative. Not only has Dr. Moore himself taken for many years a foremost part in investigations upon this vitamin, but he has been indefatigable in collecting and collating the work of some two thousand other authors whose publications are reviewed and recorded in his very comprehensive bibliography.

The book is divided into eight parts. The first four, comprising thirteen chapters, are devoted to the biochemistry of the vitamin, its estimation by various methods, its chemical structure and its sources in nature. These chapters will prove of especial value to biochemists and others who may be interested in this branch of nutrition, for they contain a wealth of practical information. These parts are succeeded by a long one containing ten chapters upon physiology and metabolism, which in turn is followed by three parts, divided into sixteen chapters, in which the manifold pathological effects of deficiency or excess of the vitamin on man and animals are considered in great detail.

In its general plan, each chapter is more or less independently constructed as an historical essay—the sequence of relevant discoveries being traced successively from the earliest and most nebulous suggestions to the clearer and more defined concepts current to-day. A book primarily designed on such chronological lines has advantages and drawbacks. While it records the development of ideas clearly, and with fairness to many pioneers in vitamin research now in danger of being forgotten, it equally entails the perusing of much material, some of it now greatly outdated, before the current views in the particular matter are reached. The book will therefore prove particularly attractive to biochemists and physicians to whom a study of the evolutionary development of this branch of the science of nutrition presents an especial appeal. In this scholarly approach, the book is a model of clear exposition.

Dr. Moore has produced a monograph that reflects great credit on British biochemistry; it will long remain an authoritative source of information and reference upon all questions that relate to the chemistry, physiology and pathology of this important vitamin. The production of the book, which has been beautifully printed in Holland, could hardly have been improved upon, and the author and publishers are to be congratulated on the many aids to ready reference that they have introduced for the convenience of readers.

Medicine and the Navy, 1200–1900. Volume 1 (1200–1649). By J. J. Keevil, D.S.O., M.A., F.S.A., M.D., Surgeon Commander R.N. (retd.). (Pp. viii + 254; illustrated. 40s.) Edinburgh and London: E. & S. Livingstone Ltd. 1957.

It is indeed remarkable that until the present time no comprehensive work has appeared on the history of our Navy's medical service, but it is a matter for congratulation that the omission is now to be so handsomely corrected. The Wellcome Trustees have supported the present enterprise and there can be no one better qualified in every way than Surgeon Commander Keevil to carry it out.

The author has precisely the right attributes for the task in hand. A regular medical officer in the Royal Navy, he served with gallantry and distinction in the recent war, latter being responsible for the production of a new manual for sick berth attendants. Since the war he has become an historian and antiquarian of note and two delightful books "Harvey the Stranger" and "The Stranger's Son" have already appeared from his pen. His present task: to trace the story of naval medicine from 1200 to 1900 is obviously his *magnum opus* and the first volume which takes us up to the execution of Charles I is a fascinating work, a veritable source book for an immense amount of little known material and written withal, in a pleasant easy style.

No one who has had to prepare a Hurt Certificate for a naval rating could fail to be intrigued with its antecedents "The Laws of Oléron" which Henry II's Queen Eleanor brought to this country in 1154. In mediæval times, there were few provisions for the sailor who fell sick, or what was much less likely, wounded in battle. Hospitals like that of St. Mary at Chichester provided care for a few who were then tended by monks.

The old conflict between physician and surgeon found its counterpart afloat and the ship's surgeon, who for centuries professed little physick, was at a great disadvantage when so many more of his charges died from conditions allied to the inadequate victualling of ships for long voyages and so few from the wounds of naval engagements. William Clowes, in the latter part of the sixteenth century, stands out as the leading barber-surgeon author afloat but he was to leave the Navy and join St. Bartholomew's hospital staff. Clowes knew much about scurvy, one of the greatest scourges of seamen and associated it with their diet, but a hundred years earlier Richard Hawkyns, a model commander if ever there was one, had discovered "that which I have seen most fruitfull for this sicknesse, is soure Oranges and Lemmons. . . ."

This excellent book is an essential for every medical library and there can be few doctors who have served afloat who will not want to own it for themselves. The subsequent volumes will be awaited with eagerness and pleasure and the completed series will become a standard work of reference. The typography is good and the index and chronology admirable but the wide pages with their long lines of print are tiring to the eyes. If the size of volume is to remain the same it would be a real comfort to have it printed in double columns on each page.

Pelvimetry. By Herbert Thoms, M.D. (Pp. 120; illustrated. 37s. 6d.) London: Cassell & Co. Ltd. 1957.

This small book is written by an acknowledged master of the subject of X-ray pelvimetry. Within its compass it encloses detailed and comprehensive information on a subject which is now regarded as an essential part of modern obstetrics. No part of the subject is omitted. There are descriptions of the techniques of taking and interpreting X-ray pelvimetry and the clinical aspect, including the importance of taking clinical findings into account with the radiological findings, is always kept in the reader's mind.

Dr. Thoms has developed his own essentially logical classification of the basic shapes of the pelvis; this is at variance with that, perhaps better known, of Caldwell and Moloy, though from a practical point of view the differences in classification are mainly academic. There is also little to be found about cephalometry and of the fact, so essential in the diagnosis of cephalo-pelvic disproportion, of the importance of the size of the fœtal skull in relation to the maternal pelvis.

Dr. Thoms is an enthusiast for X-ray pelvimetry and recommends that at least one view of the pelvis should be taken in every primigravida. No doubt his manuscript was finished before work in this country and elsewhere drew attention to the possible dangers of irradiation of the unborn child. Many obstetricians will now feel reluctant to undertake X-ray pelvimetry except in cases where it is felt necessary on clinical grounds to have an accurate assessment of pelvic capacity, such as can only be obtained by the use of X-ray pelvimetry.

Obstetricians and radiologists will find this book of the greatest value, not least for its concise and well-written text and for its excellent illustrations.

Section of Anæsthetics

President—KATHARINE G. LLOYD-WILLIAMS, C.B.E., M.D., F.F.A.R.C.S.

[*April* 5, 1957]

Problems of Anæsthesia in Relation to Cardiovascular Surgery

By OLE SECHER, M.D.
(*Copenhagen*)

CARDIOVASCULAR surgery was started in the University Hospital, Copenhagen, about ten years ago, under the direction of Professor Husfeldt. During this decade there has been great development in this field; not only in surgery, but also in diagnostic procedures and anæsthetic technique. Diagnosis has become more accurate, new operations have been introduced, and a greater variety of heart malformations have become treatable by surgery. Anæsthetic technique has improved tremendously; new fields have been opened up by means of hypotension and hypothermia, and we have developed a safe standard technique, using superficial anæsthesia in combination with curarizing drugs; all these have contributed towards ensuring a satisfactory outcome for the patient.

The number of cases presenting for heart surgery has steadily increased over the last ten years: by January 1, 1957, there was a total of 1,005, of which 172 occurred in 1956. In this paper I shall discuss some of the problems which may be encountered in this more specialized form of surgery and anæsthesia. Table I represents a summary of the material on which our experience is based and which covers nearly all the branches pertaining to this form of surgery. In other centres, a greater total number of cardiac operations has been performed, but the field has not been so wide.

The largest section of this material is divided into three main groups: patent ductus, tetralogy of Fallot and mitral stenosis. In the other groups a large number of atrial septal defects has been treated and also many pulmonary stenoses with only one fatality. The number of aortic stenoses has been very small and the results extremely bad. Operations for the relief of coronary sclerosis have been few.

I should like to say a few words about some of the physiological principles underlying the choice of anæsthetic technique. A clear understanding of the importance of CO_2 elimination is necessary in order to provide the surgeon with the best operating conditions, and to maintain the patient in a satisfactory physiological state.

Cardiac disease can be divided into two main categories, congenital and acquired. The first can be subdivided into cyanotic or non-cyanotic. The presence of cyanosis will depend upon the pressure conditions in the right and left side of the heart and the character of the shunt. Therefore it may be seen that any excessive positive pressure used for ventilation which causes diminution of the pulmonary circulation is undesirable in a patient already suffering from a poor pulmonary circulation. For this reason we have given up completely the use of a respirator for these operations. A diminished pulmonary circulation will also result in a slowing down of the time of uptake and exchange of anæsthetic gases, and therefore it is advisable that only the rapidly acting anæsthetic gases should be used. For this reason ether has been given up completely; it also increases hæmoconcentration, and

TABLE I.—SUMMARY OF 1,005 CARDIOVASCULAR OPERATIONS PERFORMED IN THE UNIVERSITY HOSPITAL, COPENHAGEN

	Operated		Died	
	Single groups	Total	Single groups	Total
Patent ductus		280		12
Pulmonary stenosis (+Morgagni)				
Valvotomy		61		1
Tetralogy of Fallot (+Eisenmenger)				
Blalock	130		6	
Pott	6		1	
Valvotomy (open 1)	46	225	4	27
Barrett and exploration	42		15	
Cardiotomy (open)	1		1	
Atrial septal defect (4 reoperated patients)				
Søndergaard	17		2	
Bjørk Søndergaard	34		2	
Bailey	10	64		7
Exploration (open cardiotomy 1)	3		3	
Ventricular septal defect				
Dammann	12		7	
Cardiotomy (open)	2	14	2	9
Other congenital malformations				
(Transposition, aorta-pulmonary window, vascular ring, &c.)	15		6	
Cardiotomy	1	16	1	7
		660		
Mitral stenosis				
Valvotomy		240		22
Aortic stenosis				
Valvotomy		2		2
Constrictive pericarditis				
Pericardiectomy		27		8
Coronary sclerosis				
Arnulff	3			
Vineberg	2	5		
Coarctation of the aorta				
Resection		71	71	10
		1,005	731	105

this is an undesirable side-effect in a patient with a very high hæmoglobin, such as may occur in cases of tetralogy of Fallot.

Maintenance of effective ventilation of the patient is difficult during certain parts of cardiac operations, firstly on account of the collapsed lung, and secondly due to the effects of a partial or complete clamping of the pulmonary artery in a patient already suffering from an inadequate lung circulation. Furthermore the delicate surgical work in progress demands that movements of the mediastinum shall be minimal. Therefore, for children, a special anæsthetic technique is used in which a rapid, small-pressure ventilation of from 40–60 per minute is maintained by means of specially designed equipment (Secher and Nyrop, 1955), utilizing a closed "to-and-fro" system with absorption ensuring a very small "dead space". Measurements of body temperature during the use of this equipment have shown that no elevation occurs—even on a warm summer day.

Anæsthesia is normally induced in adult patients by giving a barbiturate intravenously; when sleep ensues N_2O is added using either a "to-and-fro" or a circle system. Relaxation is obtained with curare, Flaxedil or Laudolissin. With regard to the more specialized anæsthetic apparatus an electrocardiograph working in combination with an oscilloscope is considered necessary. Also of great importance is an electric defibrillator and an electric thermocouple to measure temperature. A capacity manometer is used for assessing the results of the surgery during the course of the operation. All this apparatus is mobile and can easily be transported on one trolley.

Patients with a high hæmoglobin tolerate thirst badly and are therefore operated upon early in the day. Patients with pericarditis should have the chest aspirated before commencement of anæsthesia. Digitalization is only carried out if considered essential. For the

majority of cases we use morphine-atropine premedication, and complications from this have not arisen (Baden *et al.*, 1955).

Cyclopropane is the anæsthetic of choice for children following induction with nitrous oxide. We usually carry out induction with the child sitting up. The use of the curarizing drugs is restricted to older children and adults. The reasons for this choice of anæsthetic technique are, firstly, that with cyclopropane it is always possible to have the patient fully conscious at the conclusion of the operation and, secondly, we find it difficult to calculate the dose of curarizing drugs necessary for the small child, also we wish to avoid the use of atropine and neostigmine post-operatively. The latter criterion applies also to adults. During operation we avoid the use of additional drugs (such as procaine, quinidine, &c.) apart from those used for the treatment of cardiac arrest. After the thorax is opened, blockage of the vagus on the same side as the operation is carried out with local analgesic.

One result of the development of cardiac surgery is that a substantially larger number of poor-risk cases come for surgery. This is seen especially in the case of children under one year having exploratory thoracotomies, pleural patent ductus cases with a high pulmonary pressure, and in the number of reoperations.

A number of patent ductus cases have been operated upon under hypotension, and some of the worst-risk patients have undergone hypothermia. Hypotension has been used for coarctation operations with excellent results.

The difficulties encountered when undertaking anæsthesia for the patient with cardio-vascular disease are often fewer in number than might be expected in these poor-risk patients. On the other hand when complications do arise, they will as a rule be of a more serious nature than those commonly met with in other branches of surgery. Some of the frequently occurring problems may be classified as follows:

(1) *Apparatus.*—Very often we are called upon to treat babies and very small children, and here special baby-equipment is required which reduces "dead space" to a minimum if complications are to be avoided. The technique used is of less importance, but it is vital that a free airway and adequate ventilation be maintained.

(2) *Anæsthetic complications.*—Most patients tolerate anæsthesia exceedingly well and when difficulties arise they are most commonly related to ventilation rather than to the actual anæsthesia. Frequently patients suffering from the more severe forms of heart disease will be better oxygenated under anæsthesia than in either the pre-operative or post-operative period. One complaint arising from the use of light plane anæsthesia and curare technique has been that some patients have said that they were awake during the operation, although they did not experience pain.

A fall in blood pressure is tolerated badly during cardiac surgery, especially when the cardiac reserve is small, but if possible we try to avoid the use of drugs in the treatment of this condition. Suspension of the operation and gentle inflation of the lungs is often sufficient. This sudden occurrence of hypotension is frequently seen when turning the patient at the start or end of the operation.

(3) *Free airway.*—Cases of vascular ring present a problem in the maintenance of a free airway because obstruction of the very soft trachea easily arises during the dissection. Lung œdema occurring during anæsthesia and operation has not been seen.

(4) *Cardiac function.*—Under this heading, or under that of cardiac arrest occur most anæsthetic errors of judgment, but it does not often prove possible to isolate these from other contributory factors. Poor heart action may result from inadequate ventilation performed with too high a pressure (this combination caused one of our deaths), overdosage of anæsthetic drugs, pressure on the heart, herniation of the heart through the pericardium, clamping of vessels and hæmorrhage. Anoxia and retention of carbon dioxide are also important. Poor cardiac function will usually improve if the operation is stopped and the lungs gently inflated.

(5) *Cardiac arrest.*—We have seen a large number of cases of cardiac arrest and although reluctant to obtain experience in this field, we have learned a great deal about the treatment of this condition. As a rule one can say that if cardiac arrest occurs where valvular stenosis is present, completion of the valvotomy is essential before any other treatment is attempted. Heart massage should be commenced at the earliest possible moment and further treatment will depend upon the condition of the heart in each individual case. We have achieved success with cardiac massage alone, with calcium chloride alone, or in combination with procaine and adrenaline; ventricular fibrillation has responded to the use of the electric

defibrillator and in 22 cases we succeeded in making electrocardiographic recordings during the period of cardiac arrest. [Examples were shown.]

(6) *Surgical complications.*—Hæmorrhage is by far the most dangerous complication. It may arise as a result of sutures cutting out, ligatures slipping, or directly from the rupture of vessels or myocardium. Maintenance of the blood volume presents the biggest difficulty. We prepare for this eventuality beforehand by setting up two intravenous drips, and by this means it is possible to give a large quantity of blood in a very short time. For example, in one case where an aortic aneurysm ruptured 11 litres of blood were given in twenty minutes.

(7) *Transfusion.*—Determination of blood loss during operation is often a major problem, especially when operating upon very small children, or when severe hæmorrhage occurs. In cardiac disease it is only too easy to give excessive amounts of blood or fluid. In our series there occurred two cases where one of the main factors leading to a fatal result was overtransfusion. During one period we attempted to estimate blood loss by swab washing; this method gave good results and helped to train the staff in estimating blood loss. Unfortunately, we were forced to abandon this method due to the laborious nature of the technique. The development of a rapid and accurate technique for the estimation of blood requirements during operation would be an invaluable aid to this type of surgery. We commonly find difficulty with blood from the bank as it seems to block the filters in the giving sets very easily; this may occur at a vital moment. As a rule we use percutaneous drips for adults, but in small children cut down on a vein and insert a polythene catheter. When urgent transfusion is required a form of roller pump is used.

(8) *Post-operative complications.*—Apart from the post-operative conditions common to any type of surgery, the main complications following cardiovascular surgery appear to be emboli, hæmorrhage (especially after Barrett's operation), cardiac insufficiency and difficulties in maintaining fluid balance. Manual ventilation in the immediate post-operative period may prove necessary, as respiratory insufficiency and the patient's inability to cough are likely to give rise to pulmonary complications. In cases of congenital heart disease relatively large doses of morphine post-operatively are advisable as uncontrolled pain will cause a build-up of "pressure respiration", accompanied by severe cyanosis, which must be avoided. In the case of patients operated upon for mitral stenosis, the circulation is unable to stand large quantities of fluid in the post-operative period, and only the very minimum which will maintain the patient in fluid balance should be given. If the operation has proved successful, the circulation will soon be able to mobilize the fluid in the tissues. A special group of patients are those who suffered anoxia during the operation; these were usually cases in which a period of cardiac arrest had occurred. I should like to illustrate this point with two short case histories; the difficulty of giving a prognosis in these cases will also be seen.

Case I.—Thoracotomy and valvotomy were performed upon a 48-year-old woman. Anæsthesia consisted of a barbiturate and nitrous oxide supplemented by Scoline and Laudolissin. Before the valvotomy, measurement of the pressure in the left atrium and ventricle was carried out by means of a capacity manometer. It proved impossible to perform a valvotomy by means of the finger alone, consequently a valvotomy saw was used. During this manœuvre, which occupied nearly five minutes and proved extremely difficult, a severe hæmorrhage occurred, the action of the heart became inadequate and cardiac arrest followed. Cardiac massage was immediately instituted, and 5 ml. of 10% calcium chloride was given to help maintain the tone of the heart muscle. This dose was repeated twice, and cardiac activity then became normal again. Cardiac massage had been given in all for twenty-two minutes.

Post-operatively the patient was unconscious, her left arm was limp and paralysed, the right arm flexed and spastic and small jerking movements were present in the right leg. Ten days later the patient reacted slightly to noise, but no contact could be made with her. After one month an improvement could be seen. She was more awake, but was still unable to answer questions. She could say separate words, but they had no connexion with the question asked. Two months later the patient was talking complete nonsense and having hallucinations. After five months she was swearing like a trooper, but had become more rational and orientated. Six months after the operation the patient could walk, but the extremities were somewhat spastic and the range of movements limited. She now began to develop aggressive tendencies. The question of an operation for her mental condition was discussed, but the idea was abandoned as it was thought that nothing useful would be achieved. The patient was discharged home eight months after the operation.

Case II.—A 10-year-old girl with pulmonary stenosis underwent a transpulmonary valvotomy using a "by-pass" technique, by means of a catheter which takes the blood beyond the stenosed part of the artery, while the clamps are on and the valvotomy performed.

Anæsthesia was induced with nitrous oxide and maintained with cyclopropane utilizing a closed system (to-and-fro); 10 mg. Laudolissin was given for additional relaxation.

After the by-pass catheter had been inserted, clamps were placed on the pulmonary artery and three to four minutes later the pulmonary artery was opened and remained open for about two minutes. At this time the pupils were of medium size. Ten minutes after the artery had been clamped, cardiac arrest occurred. Treatment by cardiac massage was immediately commenced and the by-pass catheter was removed. The pupils were beginning to dilate and five minutes after the onset of cardiac arrest were maximally dilated. 10 ml. of calcium chloride were given for maintenance of cardiac tone. Now came the onset of ventricular fibrillation and the electric defibrillator (1·5 amp., 0·5 sec. ×2) was used four times, but without effect. 6 ml. of 1% lignocaine were now injected, followed by 4 mg. adrenaline, and then again 5 ml. of lignocaine; a further shock was given with the defibrillator using 1 amp. 0·15 sec., and the heart returned to normal rhythm.

Post-operatively, the patient had twitchings of the extremities, was unconscious, pale and cyanotic, but the corneal and pupillary reflexes were present and she reacted to pain. Cooling was instituted in an attempt to reduce the cerebral effects of the anoxia which had occurred during the operation and also in order to prevent a further rise in temperature. The lowering of the body temperature was accomplished by means of ice, cold water, and fans, supplemented with Phenergan and pethidine. When the temperature had been lowered to 29·9° C., the patient's condition was seen to have improved. During the night the temperature rose slowly to around 36°C., and at this level there came rhythmical twitchings in the patient's left arm and leg. This was controlled with barbiturates and pethidine intravenously. The following morning the patient was still unconscious but we were able to remove the tube. Only isolated twitching movements were occurring now in the leg, and these could be controlled with intramuscular pentobarbitone. Her condition continued to improve during the day until in the evening she could be contacted sufficiently to answer questions adequately including remembering her age and birthday. The twitching in the left hand ceased, but the child seemed dazed and slow to react, and complained somewhat. However, a closer examination revealed that she had been in a similar state before the operation. Her mother is mentally defective. A psychiatric examination was carried out on the child, but did not reveal anything of importance, and she was discharged in good condition.

I should like to say a few words relating to our experience with hypotension and hypothermia. Hypotension was used in 16 cases of patent ductus, in which prior to operation there was a high pressure in the pulmonary artery and also for 34 operations for coarctation. In the former group 3 deaths occurred, but in the latter only 1. There are two main indications for the use of hypotension in an operation for patent ductus arteriosus. Firstly, in order to reduce the pressure in the ductus itself, and so minimize the risk of bleeding or rupture during the course of the dissection and ligation or division; secondly, to reduce the pressure and improve blood flow in the pulmonary circulation. The results obtained have been very satisfactory to the surgeons, but as I have stated there were 3 deaths in this group.

Recently we have tried in 2 cases to combine the use of hypotension during operation with pre- and post-operative dehydration; this apparently has given good results. Out of a total of 12 deaths occurring in the patent ductus group of operations, 8 of the patients had pulmonary hypertension prior to operation. These cases are definitely a poor risk, and some of them are quite unable to tolerate clamping of the ductus, as it appears to act as a safety valve.

In coarctation of the aorta the systolic blood pressure is often 200 mm.Hg and during the operation it may rise even higher, to be followed by a sharp fall when the anastomosis is established.

Induced hypotension is of great value in these cases, and in a typical instance where it was employed the blood pressure remained around 100 mm.Hg during the whole of the operation, only rising slowly in the post-operative period. We have not seen a case of kidney complication arising from the use of hypotension, and in the series there was one death (Secher *et al.*, 1956).

Hypothermia has been used on 23 occasions but was reserved for the very poor risk cases of which the largest group — 10 — had atrial septal defects (Fig. 1). One-third of these patients died and almost as many developed ventricular fibrillation during operation.

We found this latter condition difficult to treat in the hypothermic patient, and achieved no success either with drugs or the defibrillator until the œsophageal temperature had been restored to 32°–34° C. This was achieved by pouring about 150 litres of warm saline into the open thorax (Fig. 2) (Husfeldt and Secher, 1956).

In our department we have virtually abandoned the use of hypothermia; it did not prove as successful as we had hoped and the production of bradycardia was the only real advantage. Operations upon atrial septal defects can be carried out with greater safety without the use of hypothermia and the results obtained by using the closed method are just as satisfactory.

Of the 1,005 cases reviewed here 105 died (about 10%) and the main factors relating to the cause of death are set out in Tables II–VII, which are largely self-explanatory.

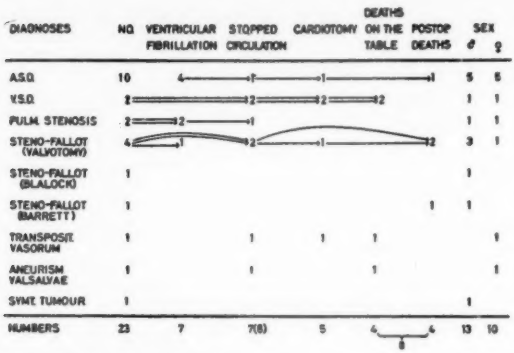


FIG. 1.—Records from the patients treated with hypothermia during operation. Each arrow represents one patient. By following the arrows the progress of each individual patient may be seen.

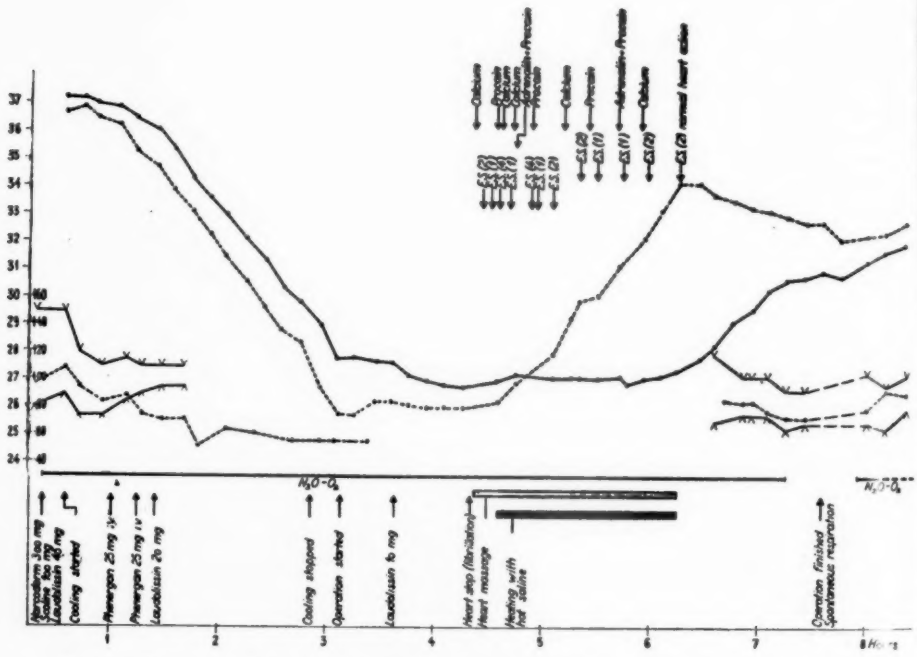


FIG. 2.—Temperature curve (continuous line, rectal; dotted line, œsophagus) blood pressure and pulse curve for one patient, a girl aged 17 with an atrial septal defect, who was operated on under hypothermia. Treatment of the ventricular fibrillation is shown on the figure.

(From: Husfeldt and Secher (1956) by kind permission.)

Table II shows the results in the patients who died, and it can be seen that the poorest results were obtained in those patients whose circulatory condition was little, if at all, improved by the operation. Furthermore the largest part of this group consisted of those cases of congenital heart disease operated upon during the first year of life, many of whom had multiple complicating malformations. In the mitral stenosis group the highest death-rate was found in those who had superimposed calcification of the valve; their average age at death was 45.

TABLE II.—PRELIMINARY ASSESSMENT OF OPERATIVE PROCEDURES RESULTING IN MORTALITY

	No correction	Partial correction	+ correction	Pathology increased		Total
Patent ductus	3	1	6	2		12
Pulmonary stenosis	1					1
Tetralogy of Fallot						
Blalock	3	3			6	
Pott				1	1	
Valvotomy	2	1	1		4	
Barrett				9	9	27
Exploration	6				6	
Cardiotomy	1				1	
Atrial septal defect						
Søndergaard	1	1			2	
Bjørk Søndergaard				2	2	
Bailey						7
Exploration	2				2	
Cardiotomy	1				1	
Ventricular septal defect						
Dammann		7			7	9
Cardiotomy		2			2	
Other congenital malformations	2	2		2	6	7
Cardiotomy				1	1	
Mitral stenosis	2	3		17		22
Aortic stenosis				2		2
Constrictive pericarditis		7		1		8
Coarctation of the aorta	1	3	3	3		10
	25	30	10	40		105

TABLE III.—DEATHS GROUPED ACCORDING TO AGE

	⩽3 years	3–15 years	⩾15 years	Total
Patent ductus	3	4	5	12
Pulmonary stenosis	1			1
Tetralogy of Fallot				
Blalock	1	4	1	
Pott	1			
Valvotomy	1	1	2	
Barrett	8	1		27
Exploration	3	2	1	
Cardiotomy		1		
Atrial septal defect				
Søndergaard		2		
Bjørk Søndergaard			2	
Bailey				7
Exploration		1	1	
Cardiotomy	1			
Ventricular septal defect				
Dammann	7			9
Cardiotomy	2			
Other congenital malformations	3	1	2	7
Cardiotomy	1			
Mitral stenosis			22	22
Aortic stenosis			2	2
Constrictive pericarditis			8	8
Coarctation of the aorta	1	4	5	10
	33	21	51	105

28 < 1 year

TABLE IV.—RELATIONSHIP BETWEEN OPERATION AND TIME OF DEATH

	Deaths during operation	Deaths occurring during 1st 24 hours post-op.	Deaths occurring up to 8 days post-op.	Deaths occurring after 8 days
Patent ductus	2	4	3	3
Pulmonary stenosis		1		
Tetralogy of Fallot				
Blalock	1	3	1	1
Pott		1		
Valvotomy	1	1	2	
Barrett	6	13	6	2
Exploration	3	6	1	1
Cardiotomy		2	1	
Atrial septal defect			1	
Søndergaard	1			
Bjørk Søndergaard		1	2	
Bailey	3			
Exploration	2			
Cardiotomy		1		
Ventricular septal defect				
Dammann	1	2	4	
Cardiotomy	2			
Other congenital malformations	1	2		3
Cardiotomy	1			
Mitral stenosis	2	5	14	1
Aortic stenosis	2			
Constrictive pericarditis	1	3	2	2
Coarctation of the aorta	2	5	2	1
	23	37	33	12

Tables III and IV show the same 105 deaths grouped according to age and interval between operation and death; Tables V, VI and VII show the incidence of complications which occurred in these patients before, during and after operation respectively.

TABLE V.—PRE-OPERATIVE COMPLICATIONS

		Complicating malformations	High pulmonary pressure	Previous operations
Patent ductus	..	4	8	1
Pulmonary stenosis		1		
Tetralogy of Fallot				
Blalock	.. 1			1
Pott	.. 1			
Valvotomy	.. 2	14		
Barrett	.. 8			1
Exploration	.. 1			3
Cardiotomy	.. 1			1
Atrial septal defect				
Søndergaard	.. 2			
Bjørk Søndergaard				
Bailey	.. ..	4	1	
Exploration	.. 1			1
Cardiotomy	.. 1			
Ventricular septal defect				
Dammann	..		6	
Cardiotomy	..	1	1	
Other congenital malformations		1		1
Cardiotomy	..	1		
Mitral stenosis	..	7		1
Aortic stenosis	..			1
Constrictive pericarditis	..	1		
Coarctation of the aorta	.. ..	3		
		37	16	8

TABLE VI.—COMPLICATIONS DURING OPERATION

	Poor heart-action	Cardiac arrest	Surgical complications	Deaths on the table
Patent ductus	1	4	3	2
Pulmonary stenosis	1			
Tetralogy of Fallot				
Blalock		2		1
Pott				
Valvotomy		1		1
Barrett	1	1	1	1
Exploration	1	4	2	3
Cardiotomy		1	1	
Atrial septal defect				
Søndergaard		1		1
Bjørk Søndergaard			1	
Bailey		4		3
Exploration		2	3	2
Cardiotomy		1	1	
Ventricular septal defect				
Dammann		2		1
Cardiotomy		2		2
Other congenital malformations		2	1	1
Cardiotomy		1		1
Mitral stenosis		3	2	2
Aortic stenosis		2	1	2
Constrictive pericarditis		1	1	1
Coarctation of the aorta		2		2
	4	32	13	23

TABLE VII.—POST-OPERATIVE COMPLICATIONS

	Emboli	Cardiac insufficiency	Hæmorrhage (rupture, ineffective suturing)	Common post-operative complications
Patent ductus		5	1	3
Pulmonary stenosis		1		
Tetralogy of Fallot				
Blalock	3	1	1	
Pott		1		
Valvotomy	1	1		
Barrett	5	7	2	
Exploration	1	2		
Cardiotomy		1		
Atrial septal defect				
Søndergaard		1		
Bjørk Søndergaard	2			
Bailey				
Exploration				
Cardiotomy				
Ventricular septal defect				
Dammann		6		
Cardiotomy				
Other congenital malformations		4		2
Cardiotomy				
Mitral stenosis	17	2		1
Aortic stenosis				
Constrictive pericarditis	1	5		1
Coarctation of the aorta		5	3	
	25	42	6	7

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ADDENDUM

Section of Surgery, October 1957 *Proceedings*, Vol. **50**, No. 10. **Mr. A. P. M. Forrest:** *Yttrium* 90 *Implantation of the Pituitary*

p. 864. After line 25 *insert:* "18 of the 34 patients treated by yttrium 90 implantation were considered fit for adrenalectomy and were included in a parallel series of cases treated by either adrenalectomy or pituitary implantation, by random selection. Only 5 of these 18 patients have so far shown remission of disease. 11 patients were unfit for adrenalectomy and excluded from the series—2 derived benefit.

"None of 4 patients . . ."

SHERRINGTON MEMORIAL LECTURE

Chairman—Sir CLEMENT PRICE THOMAS, K.C.V.O., F.R.C.S.
(President of the Royal Society of Medicine)

delivered on November 27, 1957

The Analysis of the Nervous System

By The Right Hon. LORD ADRIAN, O.M., F.R.S., M.D., F.R.C.P.

CHARLES SCOTT SHERRINGTON was born one hundred years ago and we meet to-night to honour his achievements by a commemorative lecture—the first of an annual or biennial series. I shall not try to express both the pride and the apprehension which I feel as the first of the long line of Sherrington lecturers who will exhibit some aspect of him to posterity. The picture that will be drawn of him may become more stereotyped and legendary as one generation of lecturers succeeds another and in the end there may be no more than a faint outline in black and white. For many of us here the picture is still full of colour and lively detail. No doubt much of it would dissolve if we tried to set it down; and our pictures would not all agree, their colours and outlines have been distorted already by our own prejudices. But at least it is our good fortune to have more than a legend to turn to: we can speak of a friend, not merely of an eminent figure in the scientific Pantheon. We must do what we can therefore to ensure that the legend does not leave out what should be remembered. It must do justice to the inspiration which Sherrington gave to Neurology. We are entitled to speak of it, for we were the younger generation who should have sat at his feet, if he had ever been willing to admit his seniority. Though we cannot go back to the period when his work took shape we have warm memories of the scientist we commemorate and of the way he lived when his work was in full swing.

He lived so long that I for one can claim to have known him for thirty years and to have known of his work for forty, although he had become a professor fifteen years before I became a medical student. He aged so little and seemed so much our contemporary that he would startle us at times by describing some episode which called up a picture of Victorian London with horse-drawn traffic and portly gentlemen with beards and top hats. One such occasion will be remembered by those members of the Physiological Society who were at a wartime meeting in Cambridge in 1940, for after the dinner at Trinity we asked him to speak to us about the meetings he had attended as a young man in the eighties. It is a pity that we had no tape recorder handy to take down his talk, but we can console ourselves by reading the letter, published in *Nature*, in which he described an emergency journey with the first samples of Diphtheria Antitoxin prepared in England to the bedside of a small boy at Lewes. It was in 1893 or '94 when he was Superintendent of The Brown Institution in London. There is no time to quote it all, though I should have

liked to do so, for it is a good example of the vivid word painting which illumina es his prose and his verse.

> "Dr. Fawssett of Lewes was waiting in a dog-cart at the station. I joined him carrying my awkward package of flasks, &c. He said nothing as I packed them in, but when I had climbed up beside him, he looked down, and said 'You can do what you like with the boy. He will not be alive at tea time.' We drove out to the old house; a bright, frosty morning. Tragedy was over the place, the servants scared and silent. The boy was very weak; breathing with difficulty; he did not seem to know me. Fawssett and I injected the serum. The syringes were small and we emptied them time and again. The doctor left. I sat with the boy."

By the afternoon the boy was better and two days later Sherrington went back to London and he and his colleague Ruffer thought that Lister should be told. "The great surgeon (not Lord Lister then) had visitors, some Continental surgeons to dinner. 'You must tell my guests about it', he said, and insisted—and so we told them in the drawing-room at Park Crescent."

The bare record of his career shows us a man who rose to scientific eminence by the accustomed route. He was at school at Ipswich, started medicine at St. Thomas's Hospital in 1876 and then went to Cambridge in 1879. He entered Caius in 1880, finished his medical course at St. Thomas's and began physiological research in the Cambridge laboratory with Langley. He was made Superintendent of The Brown Institution in 1891, Holt Professor of Physiology at Liverpool in 1895, and Waynflete Professor at Oxford in 1913. He was President of the Royal Society from 1920–25, received the Order of Merit in 1924 and the Nobel Prize in 1932. He retired from Oxford in 1936, after the death of his wife and moved to a house at Ipswich. During the war, when he was homeless, he came back to Cambridge and stayed with the Master of Caius and Mrs. Cameron. He spent his final years in a nursing home at Eastbourne crippled to some extent with rheumatism but with no other serious infirmity. He died without warning in 1952.

The record of his scientific work runs parallel with that of his academic status. His earlier papers make valuable additions to the physiology and anatomy of the nervous system but do not reveal a general plan of attack. This became evident when he held the Chair at Liverpool and when he was 49 the publication of his Silliman Lectures at Yale established it as the key to a new outlook on nervous control. This book, "The Integrative Action of the Nervous System", sums up the general methods and ideas which guided him in all his later work. It led to wider implications and more detailed analysis, but what he did afterwards at Liverpool and Oxford supplied fresh evidence but did not demand any revision of the original design.

The Simple Reflex

Reduced to essentials his plan of attack was to explore the central nervous system by devising the time-honoured form of experiment in which only one influence at a time is allowed to vary. The central nervous system might have been expressly designed to baffle such experiments, for it is there to be influenced by every circumstance which can matter to the organism. It is continually receiving messages from many sense organs and sending orders to many muscles. Sherrington's plan was to reduce this complexity by studying some very simple response which could be made to occur in isolation. By eliminating all the higher controlling regions of the brain and brain-stem the spinal cord was left able to carry out particular limb movements in response to particular sensory stimuli. These simple reflexes were still further simplified by isolating single muscles and nervous pathways and in the end the experimenter was left with a preparation in which the response would follow the stimulus with mechanical precision Comparison of such a reflex response with the twitch of an isolated nerve-muscle preparation showed the differences introduced by the more elaborate pathway through the spinal cord.

He found that conduction across the junctional regions was more readily disturbed by adverse conditions, fatigue, oxygen lack, &c., and in reflex pathways in general there was a less exact correlation between the time of commencement and ending of the stimulus and of the response. These differences were shown to depend on the synaptic junctions in the spinal cord and not on the quality of the nerve fibres leading to or from them. In this way the characteristic properties of the reflex pathway could be established and it was then possible to build up from the simple reflex contraction of the muscle towards the whole pattern of behaviour in the intact animal.

Excitation and Inhibition

One of the most important differences which Sherrington found between conduction in the reflex arc and in the nerve-muscle preparation was that a volley of sensory impulses could arrest activity in some of the motor nerve cells of the cord besides arousing it in others. It could inhibit as well as excite and in general the reflex contraction of one muscle would always involve the relaxation of those opposing the movement. It was this "Principle of Reciprocal Innervation" which opened the way to the further advance from the simple to the complex. It was the clue to the whole system of traffic control in the spinal cord and throughout the central pathways.

Sherrington's attack was bound to leave some strong points still holding out and the nature of the inhibitory effect had to be left until more was known about the properties of the synapse. There was then no clear evidence about the physical and chemical events which take place when the afferent impulses reach the end of their own pathway and cause the rise or fall in the activity of the pathways leading from it. Sherrington could safely leave these molecular problems to the younger generation who could use the latest techniques of biophysics and biochemistry. His own interests were more with the problems of integrated activity and he was content to leave excitation and inhibition where he found it.

It is encouraging, however, to know that the attack on the synapse has already reached a new position thanks to Sir Henry Dale and his colleagues and recently to one who was a pupil of Sherrington at Oxford. By the use of micro-electrodes Eccles has recorded the potential changes in the motor nerve cells of the cord. He finds that whereas excitation involves the expected decrease in the polarization of the cell membrane—the change which leads to activity—inhibition involves an increased polarization and so a higher threshold. How this change is brought about by the afferent neurones is still uncertain, but the chemistry of the junctional region may soon provide the answer.

The Control of Posture

When he passed from the simplest responses to the more elaborate, Sherrington was faced with a wide choice and had to select particular examples which would be favourable to analysis. Those which proved most illuminating were the scratch reflex of the spinal animal and the postural reactions of the decerebrate. The former was an example of a reaction which could be carried out by the spinal cord alone, but involved widespread excitations and inhibitions at many levels and great variety in the action of the limb muscles. But it was his investigation of decerebrate rigidity which led him farthest. It revealed the factors operating to give a smooth control of the muscular system and we are still finding fresh evidence of its importance.

His early work on neuro-anatomy had prepared the way and when he was established at Oxford the attack was concentrated on this theme. It was pressed home with improved techniques and enthusiastic pupils and it was a fitting sequel to the wider surveys he had made before. It showed that the ideas set out in his book retained their value for the details of reflex co-ordination as well as for the general plan.

The Stretch Reflex

This work at Oxford on the stretch reflex is so well known that I need not describe it at length. The decerebrate animal extends its legs rigidly and they resist efforts to bend them, although the degree of rigidity can be modified by the position of the head and trunk in space. The animal, in fact, maintains the steady contraction of the extensor muscles which would keep it standing if the brain-stem had not been divided. Magnus had shown how the general pattern of rigidity was modified by the signals reaching the vestibular nucleus from the otolith organs and he had been led from this to a masterly analysis of the control of posture and locomotion in the intact animal. Sherrington turned to the individual muscles and studied the effect of varying the pull on the extensors of the thigh. In the decerebrate animal these maintain a persistent steady activity which adapts itself to a varying load, so that the muscle changes its length much less than it would do if the nervous control had been cut off. The control was found to depend on the sense organs in the muscle which Sherrington had studied long before, the muscle spindles in particular. These signal the tension at each moment and their signals set up the answering reflex by which the muscle resists the change in length.

A remarkable feature of this reflex was its extreme simplicity: it was confined to the stretched muscle, the motor response copied the sensory stimulus, with no long delay, no after-discharge and no fatigue, almost as though there was no break in the pathway from the sense organs recording the tension to the muscle fibres maintaining it. The motor neurones must be open to influences from other routes, for the muscle must play its part in all the movements and postures of the limb, but it can work efficiently because the mechanism of the stretch reflex ensures that its contraction will be precisely adjusted to the changing demand.

The importance of this mechanism for adjusting the flow of impulses sent out to each muscle or to each motor unit in it has become even more clearly established by recent work. Sherrington emphasized its value in assisting the smooth transition from one motor activity to another and he was ready to compare it with the feed-back devices used by engineers for controlling the movement of heavy machinery. The engineer, like the brain and brain-stem, must decide what ought to be done but it can be left to the local monitoring instruments and their associated circuits to ensure that the movements do not overshoot their mark or overstrain the structure of the machine. In the same way the stretch reflex mechanism plays an essential part in the execution of each movement, though it has little to do with the decision responsible for it.

When Sherrington was examining the stretch reflex the general theory of feed-back circuits had not risen to its present mathematical dignity. His treatment of the subject was on a physiological level. But recent work has shown that the physiological circuits are more highly organized than he supposed. The muscle spindle, the main source of information about the forces within the muscle, does not act merely as a passive strain gauge. Its sensitivity is under constant adjustment by the spinal centres, for there are special motor nerve fibres to the muscular part of the organ: these can vary the tension of the sensitive region independently of the variations of tension in the whole muscle. The operation of this additional control has been worked out in the laboratories of Granit and Kuffler and it can be regarded as yet another example of a general principle of sensory physiology, the principle that the sense organs would be of much less value to us if they were not constantly focused and adjusted by the central nervous system. They control its activity but they are themselves controlled by it and made more or less sensitive to suit the circumstances. The control may involve widespread movement: shading the eyes against too strong a light, turning the head to catch a sound, or sniffing to identify a smell: it may depend on special accessory muscles attached to the organ, and in some cases there is evidence of efferent nerve fibres running directly to the receptor apparatus. Even the flexion reflex of the spinal animal might be regarded as an example, for its aim is the removal of the pain receptors from the stimulus which has set them in action.

Researches on the Brain

Sherrington set out to analyse the integrative action of the nervous system. His analysis of the spinal reflexes revealed a mechanism of neurones and synapses, operating by signals with inhibitory as well as excitatory effects and adjusted by information from the muscles to give a smoothly-flowing pattern of movement. But his success at this basic level never encouraged him to feel that the same methods and ideas would do for every level of nervous activity. The simple reflex had been the key to the understanding of co-ordinated movement and posture but some other kind of key might well be needed for the understanding of what went on in the brain. At Oxford he had no time to look for it, there was still too much to be learnt about the reflex mechanism, the experiments which had to be done were always laborious and his eminence had given him other responsibilities which could not be set aside.

At an earlier period, however, he had made two excursions into the field of brain physiology. One was reported in his Silliman lectures and he referred to it again in his final summing up in "Man on his Nature". It dealt with the highest level of all, for it was concerned with the visual sensations aroused by flickering light. By arranging the light source so that the bright and dark phases could occur simultaneously or alternately in the two eyes, he hoped to reach decisions about the site and the nature of the process which gives binocular fusion. The results were clear enough but their interpretation was, and remains, puzzling, for there is too wide a gap, too much unexplored territory, between the physical stimulus and the mental experience. The other research on the brain was done at Liverpool when he was working with Graham Brown and Layton. It was a careful mapping of the motor area of the chimpanzee and an analysis of the factors which caused the map to vary in detail from one animal to another. It was found that in any one animal it was rarely possible to elicit more than a fraction of the whole range of movement encountered in a series of experiments. Apart from its anatomical aspect this research may be considered the forerunner of many later investigations on the response of the cortex to electrical stimuli. It showed the much greater plasticity of the cortical than of the spinal neurones, the deviation of the response to a pathway opened by previous use, the progressive recruitment, the varied latency, &c., but in those days, forty years ago, the present range of electrophysiological technique was far below the horizon. Sherrington had to relate stimulus to movement, as in his work on flicker he had tried to relate stimulus to sensation. Some of the intervening events can now be recorded but then they could only be inferred and there were too few data to check the inference.

Thus at the end of his active work in the laboratory the brain and its control of behaviour remained a major field for experiment. Its control of or by the mind remained what it had always been, a theme for philosophers to debate. Sherrington never reconciled himself to Pavlov's whole-hearted acceptance of brain physiology as a sufficient explanation of the mind, though he was ready to await the results of new methods of brain research.

It cannot be said that our new methods have made it much easier to follow the operations of the brain in detail. They have added a great many data concerning the activities which take place inside it, but we are still waiting for more light on the basic problem of habit formation and the related one of attention. Yet the general scheme which was so effective for the spinal reflexes is still our best guide to the factors controlling the direction of behaviour as well as its detailed integration, for there is a gradual increase in complexity as we pass from the spinal to the cerebral level and the brain-stem gives us a transitional region where general behaviour begins to show itself.

The Brain-stem Level

When the cerebrum is destroyed, leaving the brain-stem in control, the animal can stand and walk and run and if it is placed on its back it will regain the standing position. Its behaviour has no survival value. It is that of an automaton which

can do little else than stand and walk, but the standing and walking are both activities demanding a level of integration which involves the whole animal.

In fact Magnus and Rademaker were able to reduce most of these elaborate reactions to a sequence of simple reflexes. Each one is the immediate response to a particular sensory stimulus, though their combination shows an adaptation to circumstances which links them with cerebral rather than spinal reactions. Thus, in regaining the standing posture, if the normal sequence of actions cannot proceed, another sequence takes its place. An animal placed on its side will raise itself by a chain of reflexes starting by head movement controlled by the vestibular organs, but if the initial movement of the head is prevented, the body is righted by a different set of reflexes controlled by the receptors in the body wall.

The behaviour of the brain-stem animal certainly lacks all the variety and effectiveness of that of an animal with its central nervous system intact. This has survival value, for it is concerned with the activities by which the animal supports itself in its environment, the pursuit of food, the avoidance of danger, the adherence to the herd, &c. Sherrington spoke of the cerebrum as head ganglion of the distance receptors, signalling events beyond immediate contact with the body, and the difference is not merely in the sense organs which inform it. Operations carried out at this level differ not only in the kind of information which guides them but in the much greater plasticity of the structures which receive it. The cerebrum retains the mould of past activities, it can develop habitual patterns of action, so that skills can be acquired and the problem once solved can be solved again with less effort. Its reactions seem less like those of a machine because the relation between stimulus and response depends on the past as much as on the present.

Yet we can admit this great difference and still see an essential resemblance between the control of postural and of skilled behaviour. The animal without its cerebrum can rise to its feet and stand firmly on an unsteady platform. This requires a constant adjustment of the pattern of muscular contractions depending on the reflex linkage of afferent and efferent pathways with all the feed-back circuits for the individual muscles and the general control from the vestibular organs and the pressure and tension receptors. It could be imitated by an artificial controlling system working on the same principles: an elaborate design would be needed but once set up the machinery should work automatically. The setting up of the reflex system may well involve some gradual change in the synaptic pathways when the animal first acquires the power to stand, but once adjusted the nervous mechanism need not differ in essentials from that which gives the spinal animal the power to scratch itself.

The Cerebral Level

To ride a bicycle or drive a car involves the kind of skilled behaviour only possible at the cerebral level. It needs the distance receptors and the habits impressed on the cerebrum by previous activity. Some of it depends, like human walking, on acquired habits of movement. We have learnt to keep our balance on the bicycle by turning the front wheel towards one side or the other. At first we turned it through many degrees and pursued a zig-zag course. Our manipulation of the handle-bars was not linked closely enough with the signals from the vestibular organs, with a result like the shunting of an engine with an insensitive governor. But with practice the linkage has been improved and the balancing can be done by movements of the body as well as of the arms. It needs no conscious effort and we are seldom aware of what we are doing.

In riding a bicycle or driving a car, or in walking for that matter, we must avoid pedestrians and oncoming traffic and, when we have acquired a proper road sense, this too can be done almost unconsciously. Yet for these adjustments there is a far less immediate connexion between the sensory signals and the end response. Our course is guided by the patterns of light and shade on the retina. It would not be difficult to design an artificial system to guide a car along a white line in the middle of the road, to stop it at the red light and start it again at the green, but with the brain

to interpret the optical signals the control goes far beyond this. The car is steered to avoid a pedestrian, to give a wider berth to a child than to a grown up, to pass another car before the oncoming traffic makes passing unsafe. These operations demand the power of recognizing the special features in the pattern of light and shade which indicate an adult rather than a child, a fast car rather than a tractor, and the recognition must be linked with an immediate estimate of speeds and even of the probable intentions of other drivers.

Although our driving would certainly be dangerous if we gave it no thought at all, the movements we make to control the steering wheel and the accelerator pedal are seldom based on conscious judgments. A small car near at hand will give the same sized retinal image as a large car farther off, but we judge its size and assess its distance and speed without more than general awareness, certainly without deliberate thinking. Once the brain has acquired this skill or indeed any skill, most of the operations required in it seem to be carried out almost as unconsciously as breathing or walking, although they demand most of the powers of recognition, generalization and judgment that are often considered as properties of the mind.

To give the cerebrum this great extension of its field of control it has the great expansion of the cortical sheet and the great plasticity of the nervous structures in it. These at least are important differences between it and the rest of the nervous system. No doubt we shall find other less obvious factors and they may compel us to adopt some new kind of analysis, but it is important to realize that for a great deal of skilled behaviour we have no real need to consider the intervention of conscious processes. Thought is not a necessary accompaniment of intelligent action.

The Mental Level

Liddell's admirable obituary notice of Sherrington quotes him as saying "Some people think that thinking is all electric currents. Well!" He thought it something so different that it could not be fitted into the scheme of energy and matter which we use for the brain. "Thoughts", he said, ' lie outside Natural Science". In his Gifford Lectures "Man on His Nature" he is at pains to make it clear that this is a territory which neurophysiology cannot be supposed to reach.

The burden of these lectures, the final reflections of a scientist on what he had learnt, is that the reflex with all its elaborations is a conception to be used only for the material events which take place in the nervous system and that the neurologist has more than the material events to puzzle him. Yet the chapters in which he delivers this judgment are as inspiring as any in "The Integrative Action of the Nervous System". They bring no sense of failure before a goal which can never be reached. He gives full weight to our mental experiences but his discussion is constantly reminding us of how little we know yet about the material activity of the brain, of how much nearer we might come to the mental level if we knew more of the physical events linking our sense organs and our behaviour.

Some of these events are already clearer. He deals with the changes in the electrical activity of the "roof-brain" in sleeping and waking, attention and inattention. Since his book was written these have become one of the major fields of research in neurophysiology. There are new techniques which make it possible to study the activity of individual neurones in the brain during its normal working; their response to electrical stimulation has been followed with a new precision and there is a fair prospect of analysing the massive potential oscillations of the cortex in terms of dendrite and nerve cell activity. Some of this may turn out to be irrelevant, for we are still in the exploratory stage: there are a great many events in the brain which can now be recorded, beautiful instruments for doing it and a wealth of literature for reference. The difficulty is still that the conception of the reflex pathway loses its clarity when it has to be widened to include conditioned pathways; for one brain may look like another, but what it does in response to a given stimulus may be quite different because it depends on all the brain has done since it was first in action. Though we may be able to record them it will not be

easy to disentangle the physical events in the brain, so that we can tell how the analysis should proceed.

Yet there should be no insuperable difficulty, no need to go outside the framework of natural science, in analysing the cerebral activity which accompanies skilled behaviour. It is worth insisting again that actions which would certainly pass as intelligent and purposive are often done without the intervention of conscious processes. We can try therefore to reduce them to the Sherringtonian scheme without feeling that the most important link has been left out: when this has been done we shall at least be able to consider how we think with a knowledge of how the brain achieves so much when our thoughts are elsewhere. The final puzzle will still be there, but without Sherrington's insistence on it we might deny its importance and get no farther.

It is time to recall the man who faced the final puzzle so squarely. All his life he had faced problems honestly without letting his wishes dictate the answer. His honesty was for himself, it was not the kind that is used to assert superiority and justify bad manners; it gave him no pleasure to be discourteous. But more than anything else it was his honest acceptance of what he found in the world and in himself that made us look up to him.

In his old age he had many visitors at Eastbourne and it was a delight to see him and to feel that he was glad to be seen. He would talk of friends, of the books he was reading, of physiologists of the past that he had known and of his admiration for what the younger generation were doing. No one who visited him then can have left Eastbourne without renewed strength and peace of mind. Sherrington found Nature often cruel and senseless and Man no better, but he was content to face his destiny in the universal plan. He helped us by his fortitude as well as by his science. For he was a great scientist but we who knew him are fortunate in having more than his science to recall this evening.

Section of Urology

President—CUTHBERT E. DUKES, O.B.E., M.D., M.Sc., F.R.C.S.

[*June* 27, 1957]

Disturbances of Renal Physiology

By A. A. G. LEWIS, M.D.

THE kidneys are partly responsible for maintaining the volume and composition of the body fluids within narrow limits. They may fail in this task, even when perfectly healthy, when disturbances elsewhere in the body bring about changes in their function, and it is these changes that I propose to review for they properly constitute "Disturbances of Renal Physiology".

Some of the present views of the way in which the kidney elaborates urine are summarized in Fig. 1. Approximately one-fifth of the cardiac output flows through the glomeruli, where

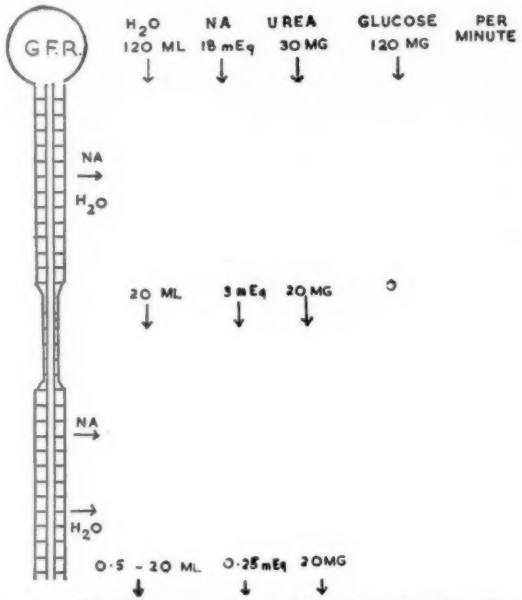


FIG. 1.—Schematic representation of filtration and reabsorption.
(*From* Lewis, 1953, by kind permission.)

roughly one-fifth of the plasma water is filtered off, with its dissolved solids. The approximate quantities of water, sodium, urea and glucose filtered per minute and ultimately excreted are shown. In the proximal tubule, seven-eighths of the filtered sodium is reabsorbed and all the glucose: as a consequence of this, it is thought, a corresponding volume of water is reabsorbed. The remarkable property of renal tubular cells of being impermeable to creatinine and almost so to urea should be noted. In the thin limb, final osmotic equilibration is thought to occur, so that the function of the glomerulus and the tubule down as far as the distal limb appears to be to supply the latter with a steady flow of some 20 ml./minute of isotonic, glucose-free, plasma filtrate. It is here that the final elaboration of the urine occurs, by a series of selective and almost independent processes of reabsorption. Sodium ions are reabsorbed and in the process partly exchanged for hydrogen or potassium ions. Sodium reabsorption can be greatly increased by the influence of aldosterone. In this part of the

tubule, water reabsorption occurs separately from that of sodium and can be varied independently of it by the activity of the antidiuretic hormone of the neurohypophysis. Two processes which, in the proximal tubule, occur together at a fixed rate, have become, in the distal tubule, independent and variable. The distal tubule also forms ammonia when extra base is needed for acid excretion.

These remarkably selective processes of reabsorption by the distal tubule may establish and maintain large gradients for the urinary constituents between urine and plasma. Urine osmolarity, for example, can be varied from less than a fourth to more than four times that of plasma; urinary sodium concentration can be reduced almost to zero, while a gradient for hydrogen ions of 800/1 can be established.

The two hormones that regulate the reabsorption of sodium and water independently by the distal tubule are aldosterone and anti-diuretic hormone (A.D.H.). Both are secreted in increased amounts in response to a fall in E.C.F. volume, and in the case of A.D.H. this has been shown to be mediated by stretch receptors in the wall of the left auricle responsive to the degree of its filling (Henry and Pearce, 1956). Both hormones, therefore, act so as to defend extra-cellular fluid (E.C.F.) volume, and, in addition, A.D.H. is secreted by the neuro-hypophysis in response to a rise of E.C.F. tonicity. An increase in the latter increases A.D.H. secretion so that distal tubular water reabsorption is increased.

Renal function may be disturbed by extra-renal influences in four ways:

(1) When renal blood flow is reduced; (2) when abnormal humoral or nervous influences modify renal function; (3) when the kidney, in carrying out one task, is prevented from performing another; (4) when there is urinary obstruction.

The renal blood flow and glomerular filtration rate are reduced when the cardiac output falls after hæmorrhage. They are reduced by pre-operative medication with morphine or pethidine and by anæsthesia, when fairly severe hæmorrhage, operative procedures or the reduction of blood pressure by ganglion blocking agents produce little further fall (Miles *et al.*, 1952; de Wardener *et al.*, 1953). Moderate falls of glomerular filtration do not have much effect on the composition of the urine. In Fig. 2, a reduction of venous return was

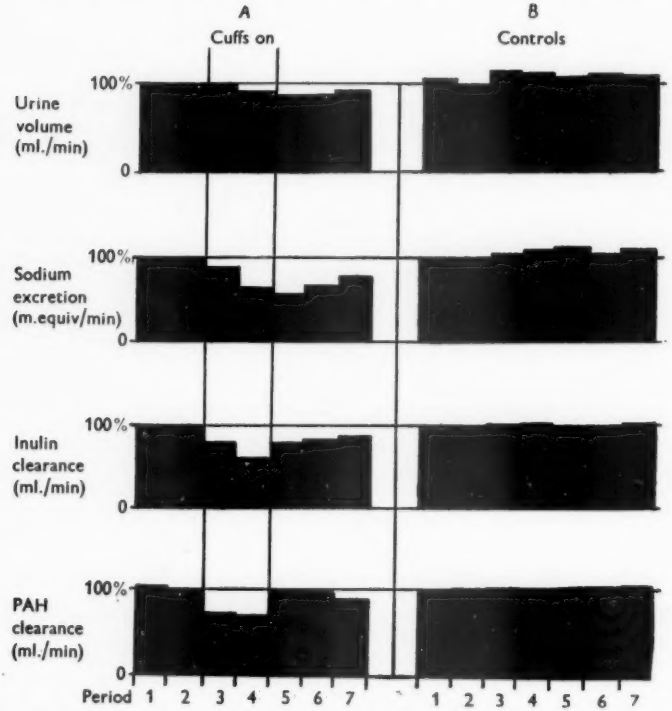


FIG. 2.—The effect of a moderate reduction of renal blood flow and glomerular filtration rate on urine volume and sodium excretion in man. (*From* Chalmers *et al.*, 1952, by kind permission.)

produced by the application of venous tourniquets to the thighs of normal subjects during sustained water diuresis. Some change in water and sodium output occurs, but this is in marked contrast to the dog, in which sodium output appears to be much more readily altered by changes in glomerular filtration rate.

Similar falls in glomerular filtration rate are produced by hypothermia, and it is significant that these are unaffected by high spinal anæsthesia. Tubular function and reabsorption may also be modified by hypothermia (Morales *et al.*, 1957).

Very severe hæmorrhage and shock produce intense renal vasoconstriction, the fraction of the cardiac output passing through the kidneys being greatly reduced (Lauson *et al.*, 1944). Though the capacity of the tubules to excrete substances such as para-amino-hippuric acid (P.A.H.) remains unaffected until the blood flow has fallen to about one-tenth of normal, distal tubular processes are suppressed and eventually no urine is formed. If intense renal ischæmia is prolonged, there is a delay in the recovery process, and if it lasts more than a few hours, tubular necrosis occurs. If this is to be prevented under these conditions, early and adequate transfusion is necessary. Where this has failed for any reason to restore the systolic blood pressure, the infusion of noradrenaline may restore renal function (Mattingly, 1957), provided that no tubular damage has occurred.

The importance of humoral and endocrine influences on renal function may be appreciated by a consideration of adrenal deficiency. Here, both glomerular filtration rate and selective distal tubular function are depressed, and can be restored by cortisone. Not only is sodium reabsorption reduced in the absence of aldosterone, but the ability of the tubule to handle sodium and water reabsorption separately is lost. Fig. 3 shows the effect of stimulating the

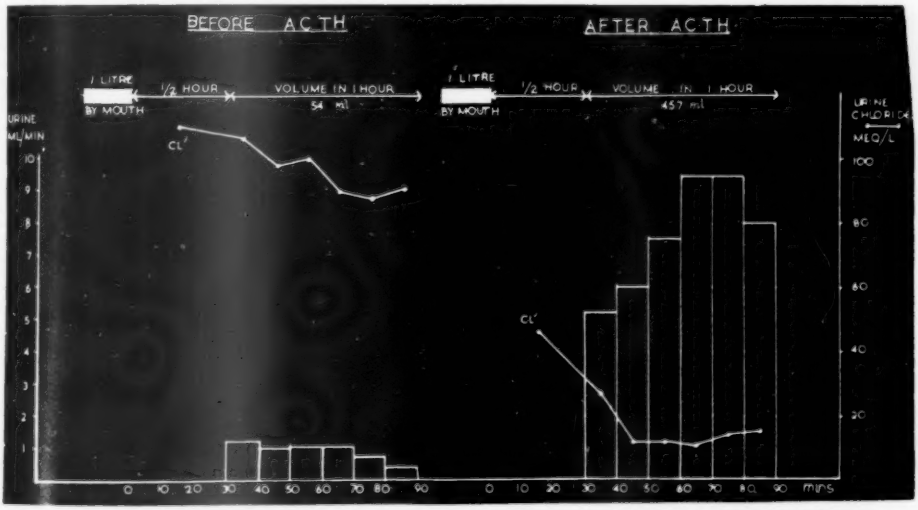


FIG. 3.—The diuretic response to a water load in panhypopituitarism before and after the administration of a course of ACTH.

adrenals with ACTH in panhypopituitarism: the ability of the kidney to produce a normal water diuresis, with dilution of the urinary solutes, in response to a water load is restored. In other words, distal tubular function has again become selective. A similar result is produced in adrenal deficiency by cortisone, but not by mineralocorticoids, which regulate sodium and potassium reabsorption only.

One interesting property of the distal tubule is its power of adaptation. On the whole, renal function in man is not greatly influenced by diet, again in contrast to the dog in which urea clearance can be greatly increased by high protein feeding. But it has recently been shown that the concentrating power of the kidney and the response of the distal tubule to vasopressin can be increased by a period of water deprivation or by a high protein or urea intake, while a period of high fluid intake reduces these responses (Epstein *et al.*, 1957).

Tubular reabsorption of sodium and water are normally related to body requirements by the varying rates of secretion of aldosterone and A.D.H. If anomalies in the production of these hormones occur, the kidney cannot make its normal contribution to homeostasis. A.D.H. will not be secreted if the posterior pituitary has been destroyed by secondary deposits,

by inflammatory changes or xanthomatosis. Distal tubular water reabsorption ceases and the patient experiences the constant water diuresis of diabetes insipidus. Occasionally, emotional disturbances lead to a suppression of A.D.H. secretion so that an emotional polyuria occurs: on the other hand, emotion, particularly that associated with fear and pain, often provokes A.D.H. secretion and emotional antidiuresis.

Both hypokalæmia and hypercalcæmia impair renal function, particularly, in the early stages, tubular function. Polyuria is a frequent early symptom of hypercalcæmia and may persist for long periods before other signs of renal failure occur. Actual deposition of calcium in the tubules and nephrocalcinosis appear to develop at a later stage, so that the condition is reversible at first. The polyuria and rising blood urea caused by hypercalcæmia may be the first signs of hyperparathyroidism, sarcoidosis, myelomatosis or of widespread secondary malignant deposits in bone.

A prolonged release of A.D.H. occurs after surgical procedures. The urine is concentrated and of low volume for many hours after operations (Fig. 4). Occasionally this

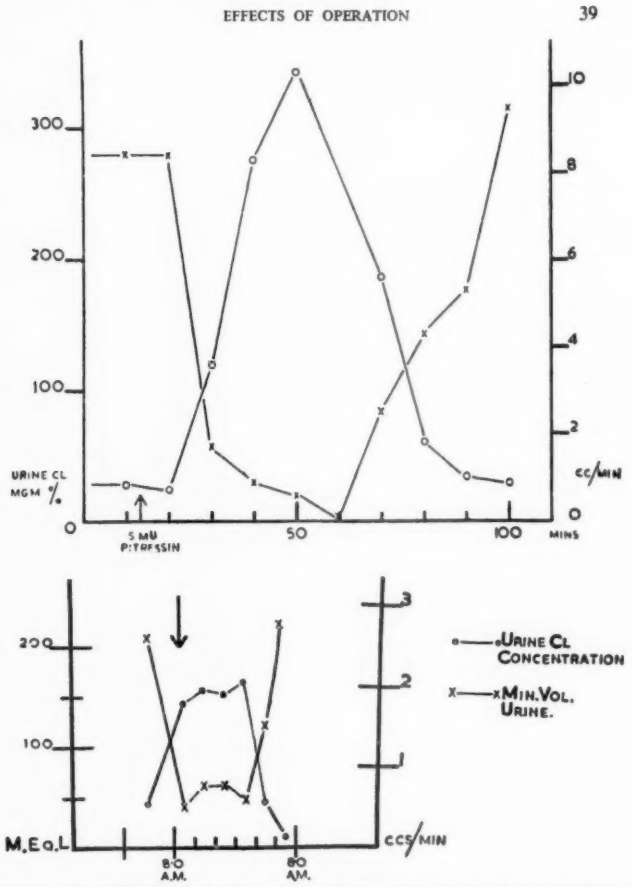


FIG. 4.—The lower graph illustrates the effect of operation (sigmoid colectomy) on the urine volume and chloride concentration, as shown by observations on four-hourly urine specimens obtained from an indwelling urethral catheter. For comparison, the upper graph shows the effect on urine volume and chloride concentration of an injection of pitressin (slightly modified from Lewis, 1953). Note that both graphs show similar changes, save that after operation these are much more prolonged.

Reproduced from Le Quesne, L. P. (1957). "Fluid Balance in Surgical Practice" (2nd edition). London: Lloyd-Luke (Medical Books) Ltd. By kind permission.

effect lasts for two or three days, when there is a risk of water intoxication if too much water is given (Fig. 5). This post-operative release of A.D.H. does not occur in response to the

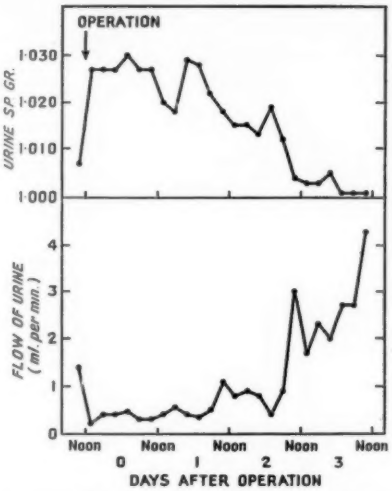


FIG. 5.—An example of prolonged post-operative antidiuresis. lasting seventy-two hours. Mild water intoxication occurred. (*From* Le Quesne, 1954, by kind permission.)

normal stimuli of changes in E.C.F. volume and tonicity. This is perhaps the outstanding example of a condition where the normal kidney is not a free agent: it is responding to an influence which is not under normal control. It follows that fluids should not be forced in the post-operative period: water should be given to replace losses occurring by the kidney, through the skin and into the gut until the abnormal secretion of A.D.H. ceases and the kidney can again excrete excess water.

Increased secretion of adrenocortical hormones also occurs after surgery. It has been reported that the urine contains increased amounts of aldosterone (Llaurado, 1955), but a recent study indicates that this only occurs when sodium intake is restricted (Hayes *et al.*, 1957). The sodium retention and potassium excretion that follow operations are usually the result of the secretion of compound F and of delay in its destruction by the liver, as well as of changes in the rate of the peripheral utilization of this hormone by the tissues.

Increased secretion of aldosterone is probably partly responsible for the renal sodium retention that causes the œdema of cardiac and hepatic failure. The production of this hormone may be increased when there is an adrenal cortical tumour, when the most striking electrolyte abnormality is the hypokalæmia produced by renal potassium loss. Hypokalæmia from any cause may produce disturbances in renal function, with low filtration rate and renal blood flow and loss of response to A.D.H. Histologically, vacuolation of tubular cells may be seen—the so-called hypokalæmic nephropathy. When the hypokalæmia is due to increased urinary loss of potassium brought about by aldosterone, the urine may be neutral since potassium and not hydrogen ions are replacing sodium ions in tubular reabsorption. But when extrarenal losses cause potassium deficiency, renal conservation of the ion occurs and hydrogen is exchanged for sodium, so that the urine is acid in spite of the systemic alkalosis of potassium deficiency.

This paradox is an example of what may occur if the kidney, having to perform one task, is thereby prevented from carrying out another. A more striking disturbance of this type is furnished by osmotic diuresis, when the kidney, called upon to excrete large quantities of osmotically active solute, fails to reabsorb sodium and water, so that dehydration results.

This is seen when the solute is glucose in diabetes mellitus, and when large quantities of urea are being excreted during high protein feeding or in the recovery stage of acute tubular necrosis. The characteristic of osmotic diuresis is the loss of the distinctive contribution

of the distal tubule, which is overwhelmed by the flood of filtrate unreabsorbed proximally: as the urine flow rises the specific gravity tends to approach that of plasma, 1010, and not, as in water diuresis, that of water.

Obstruction to the urinary outflow will obviously impose limitations upon renal function. One particular consequence, however, is worth special notice, and that is the tendency for the distal tubular response to A.D.H. to be reduced in some cases. Prostatic obstruction has been shown to be a possible cause of water-losing nephritis, the blood urea rising later, the loss of concentrating power and polyuria being corrected by removal of the obstruction (Roussak and Oleesky, 1954).

It is not easy to summarize the various instances of disturbed renal function that have been mentioned. One situation is particularly important—after a major operation the urine volume is found to be greatly reduced. Four main causes have to be considered. Pre-existing dehydration or blood loss may have been severe and not fully corrected, so that the urine is highly concentrated with high specific gravity and urea and low sodium, indicating good glomerular and tubular function. A very similar urine may be passed as a result of the usual endocrine response to surgery, and only clinical examination may differentiate this from the first situation; or severe blood loss and shock at the operation, perhaps temporarily masked by anæsthesia but becoming apparent later, may have led to urinary suppression from failure of renal blood flow and glomerular filtration rate. If this has been allowed to persist for long, acute tubular necrosis may have occurred, when the urine volume is very low—less than the minimum necessary for excretion of solutes—and, more important, the specific gravity is little raised and little modification of plasma concentration of solutes has occurred. The blood urea therefore rises rapidly. For practical purposes the kidney has now no excretory or regulatory function. I do not think that Strauss's (1948) analysis of the course of events in a 70 kg. man can be bettered. 70 grams of protein will be broken down daily as soon as carbohydrate stores are exhausted, when the combustion of 200 grams of fat will lead to the production of 470 ml. of water. Plasma potassium may rise at about 0·3 mEq./l./day if protein metabolism is halved by giving glucose, when 6 grams of N.P.N. will be formed per day, causing a rise of blood N.P.N. of 12 mg.% daily. In practice, protein destruction may be more rapid than this and is little affected by supplying further calories with exogenous fat—since this causes gastric disturbances it is better omitted. But recent work has shown that more water may be produced by metabolism than was at first realized, so that a considerable part of the daily insensible loss of 1 litre may be produced from this source. In conservative therapy, water intake should be so adjusted that a slight weight loss occurs daily.

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Section of the History of Medicine

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Introduction to Western Influences in Pre-Meiji Japanese Medicine

By GORDON E. MESTLER

Department of Anatomy, State University of New York, Downstate Medical Center, Brooklyn, New York

IT is axiomatic that the early medical practice of old Japan was a traditional inheritance of classical Chinese medicine, brought back to Japan as a consequence of Japanese military invasions of Korea. But it is believed—erroneously—by many that Japan was "closed to foreigners" until the time of Commodore Matthew C. Perry, U.S. naval officer, whose fleet steamed into Tōkyō Bay in 1853 on the peaceful mission of establishing trade relations with the Mikado's empire. Before that time there had been, in fact, communication between Japan and the Western world for nearly 300 years, with occasional interruptions. Much of the intellectual and cultural exchange during that period was of a lasting quality. Indeed, the characteristic proclivity of the Japanese for the imitation of all that is good (and some that is bad) was to lead, ultimately, to the overthrow of the feudal system which had dominated Japan through a long succession of Shōgunate governments during the Edo period from 1615 to 1867.

The present paper will attempt to give a brief sketch of Western influences in pre-Meiji Japanese medicine. The emphasis will be on the major bibliographic aspects.

News of the "discovery" of Japan in 1543 spread rapidly to Europe, and in 1549 the first Christian missionary, St. Francis Xavier, landed at Kagoshima and for the next two years travelled in various parts of Japan, particularly to the capital at Kyōto. Following this, a steady stream of missionaries from Portugal, Spain and Italy came to Japan. For our purpose here, the important fact is that these religious men were accompanied by physicians and scientists, principally naturalists. Luís de Almeida, a Portuguese "brother-doctor", is described by Asobu or Yū FUJIKAWA (1865–1940) as the first European to practise medicine in Japan. Almeida came to Japan in 1555 or 1556, and at Oita he founded a school of surgery, annexed to which was a hospital especially for sick children. Beyond this fact, the nature of his influence and its spread among those who came into contact with him is not well known.

Probably the first Western physician to make a lasting literary impression on the medicine of Japan at that early time was one Christovão Ferreira, a Portuguese, who was associated with the *Nambanji* or "School of the Southern Barbarians" which had been established in the Province of Ōmi in southern Japan, where he taught surgery to the Japanese. Ferreira is not known to have been the author of any medical or surgical books prior to his coming to Japan, but about 1600, under the assumed name of Chūan SAWANO, he wrote directly in the Japanese language a surgical work entitled *Nambanryū geka-sho*, on the teachings of the Portuguese school of surgery.

Western medicine and surgery first affected the thought and practice of Japanese physicians and surgeons by means of *oral* teachings, instructions and demonstrations provided by Western practitioners attached to various foreign missions to Japan or to foreign settlements established by permission of the Shōgunate. Such Western teachings were soon reflected in medical and surgical works composed by their Japanese pupils. Pre-eminent among these early Western physicians in Japan was Caspar Schambergen, who came to Japan in 1649 as a surgeon of the Dutch East India Company. His name identified what was perhaps the most influential Dutch school of surgery in Japan, known as "Caspar-ryū-Geka". Typical of the Japanese-written surgical works of that period was the *Geka ryōji-shu*, composed by Sōō NAKAMU, who had studied under Schambergen, a work published at Kyōto in the 2nd year of Jōykō (=1685).

Contemporary with Caspar Schambergen or immediately following his time were Willem Hoffmann, Hermanns Katz, "Danner", "Palm", "Stieven", Willem ten Rhyne, Andreas Cleyer and Engelbert Kaempfer. The clinical lectures of "Danner" and "Palm" were

preserved by one of their pupils, Hōan ARASHIYAMA (1633–1693), who wrote them out in his work entitled *Bankoku chihō tekiden* which appeared about 1675. The teachings of Schambergen were also incorporated in the *Caspar dempō*, composed by Ryōan KAWAGUCHI. In the *Almans hō-sho*, KAWAGUCHI gave an account also of the teachings of Hermanns Katz. Both of these Japanese-written surgical works appeared in 1661.

The most famous pupil of Willem Hoffmann was Chinzan or Eikyū or Shingohei or Tokitoshi NARABAYASHI (1648–1711), whose fame rests upon his translation of parts of Ambroïse Paré's *De chirurgie . . .*, from a Dutch translation by D. Carolum Battum (probably the Amsterdam edition of 1649 by I. I. Schipper). NARABAYASHI's classic work appeared in 1706 with several illustrations copied from Paré. It existed only in a manuscript (none of which is known to be extant at the present time). Fortunately, however, NARABAYASHI's manuscript, known as the *Geka sōden*, was copied by other Japanese, some parts even being stolen for that purpose. An independent semi-translation of Paré was also made by Gentetsu NISHI (1680–1760), in a manuscript work entitled *Kinsō tetsuboku ryōji* which appeared in the 20th year of Kyōhō (=1735).

Hōan ARASHIYAMA also made a copy of parts of Paré in a manuscript work known as the "Arashiyama text of Paré", probably equivalent to the *Kōi-geka sōden*. Although undated, that manuscript would predate the better known work of Chinzan NARABAYASHI in 1706, and the writer believes the ARASHIYAMA manuscript to be the earliest Japanese surgical writing which was based directly on an identifiable Western book on surgery . . . ARASHIYAMA's manuscript is still preserved in the Tōkyō University Library. Fig. 1 is a reproduction of one of the illustrations, with explanatory text, in the *Kōi-geka sōden*.

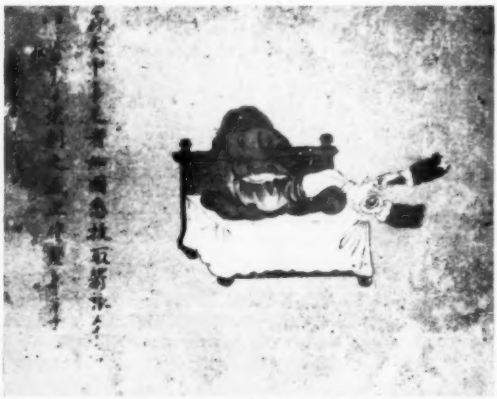
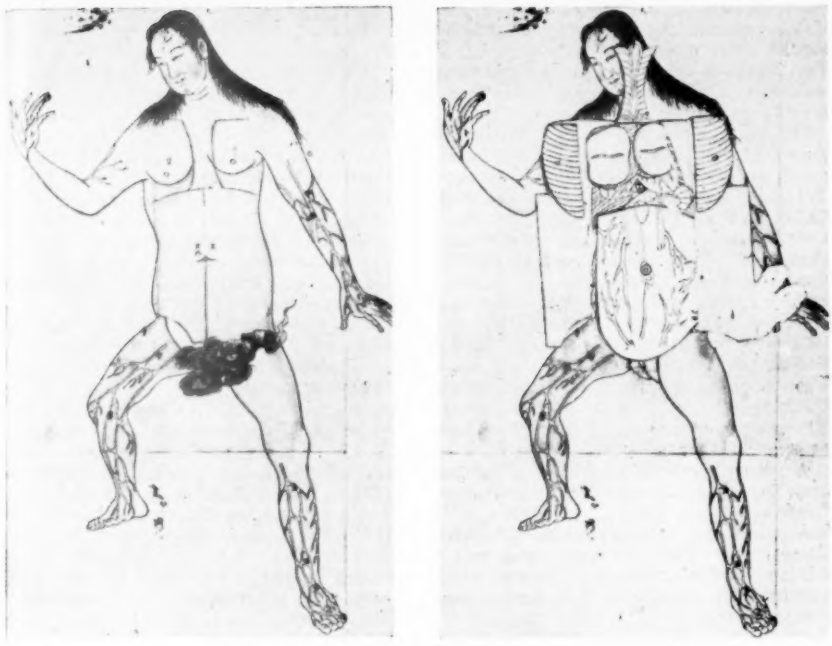


FIG. 1.—Illustration from the *Kōi-geka sōden* (n.d.), probably equivalent to the "*Arashiyama text of Paré*", manuscript by Hōan ARASHIYAMA (1633–1693). After NAGAYAMA.

The first *printed* version of the "Japanese Paré" copies was either the work known as *Geka kummō zu-i mokuroku*, by an obscure and unidentified writer, which appeared in 1764(?); or the work known as *Geka kummō zui*, by Kōhaku or Mitsuaki IRAKO (1737–1798), which was published at Kyōto in 1769 . . .

Since the dates of composition and/or publication are vague and uncertain, the distinction of being the very first Japanese medical writing to have been directly influenced by pre-existing Western medical books (as distinct from oral teachings) must be shared with the *Shokai naikei-shō*, which was a work on the nomenclature of the regions and organs of the human body that appeared in 1682, having been composed by Ryōi or Shōdau MOTOKI (1628–1697) from an unidentified Western book on anatomy. Or shared also with an anatomical atlas unique in the annals of Japanese medical works, a manuscript copy by MOTOKI based on Johann Remmelin's *Pinax microcosmographicus . . . Ontleding des menschelyke lichaems . . .* (Amsterdam, 1667), in which some of the wood-block illustrations were—like the original Western work—superimposed so that they could be folded back to reveal underlying structures. This work of MOTOKI unfortunately remained obscure following his death, until it was "rediscovered" by one Sōun SUZUKI who had it published in 1772 with the title *Oranda (or Waran) zenku naigai bungō-zu*. Fig. 2 shows a pair of the plates from this work, with the flaps in place (A) and folded back (B). MOTOKI chose to depict his figures with characteristic Oriental head and facial features.



A B

FIG. 2.—Figures in the untitled manuscript (n.d.) of Ryōi MOTOKI (1628–1697), later published as the *Oranda zenku naigai bungō-zu* (1772). A. With flaps closed. B. With flaps open.

The next important Japanese medical writing to reflect the influence of Western teaching appeared between 1742 and 1748 as the ***Oranda honzō wakai***, a work on pharmacology composed by Genjō NORO (1693–1760) who had studied under an unnamed Dutch physician at Tōkyō. The *Oranda honzō wakai* was probably the first of a series of Japanese pharmacological writings to bear the imprint of Western learning. The *Medicinae compendium* . . . (Lugd. Bat., 1731) of Johannes de Gorter is generally regarded as the first Western book on *clinical* medicine to be translated into Japanese. That work was accomplished by Genzui UDAGAWA (1755–1797) in his *Naika senyō*, which was published in 1793.

The first Japanese translation of European materia medica was made in 1828 by Genshin or Shinsai UDAGAWA (1769–1834) in his *Oranda* (*or Waran*) *yaku-kyō*, which was based upon the pharmacological writings of Adolphus Ypey, H. J. van Houte, J. Arnemann, and Christianus Ignatius Niewenhuis. Later on, the works of Karl Peter Thunberg, apparently a little-known Dutch edition entitled *Naamlyst van gewassen door den beroemden natuuronderzoeker* (n.p., n.d.); the work of Joannes Adrianus van de Water; and certain parts of an encyclopædia of medicine by Georg Friedrich Most were translated into Japanese. Also the pharmacopœias of Amsterdam, of Leyden, and of Batavia were abstracted into the Japanese language.

The anatomical atlas of MOTOKI, referred to above, was not considered important by the Japanese of that time . . . perhaps because it was overshadowed by the famous *Kaitai shinsho* in 1774, with its immediate precursor—a series of five sheets of anatomical drawings known as the *Kaitai yaku-zu* which appeared in 1773. The *Kaitai shinsho* was based principally upon Johan Adam Kulm's *Tabulæ anatomicæ* . . ., from the Dutch translation by Gerardus Dicten, *Ontleedkundige tafelen* . . . (Amsterdam, 1734). But Kulm is known to have copied the work of Philipp Verheyen, who, in turn, had imitated the plates of Andreas Vesalius' *De humani corporis fabrica*. Fig. 3 is a reproduction of the title-leaf of the atlas of the *Kaitai shinsho:* a redrawing, with alterations, of the title page of Christopher Plantin's ironical plagiarization of Juan Valverde's imitation of Vesalius, most probably the Dutch edition *Anatomie, oft levende beelden vande deelen des menschelicken lichaems* . . . (Antwerp, 1568). A set of wood-block illustrations in the *Kaitai shinsho* atlas is believed to have been copied from the Dutch edition, *Ontleding des menschelyken lichaems* (Amsterdam, 1690), of

Godfried Bidloo's *Anatomia humani corporis* . . . Certain of the works of Caspar Bauhinus, of Jan or Jean Palfyn, of Stephen Blancard, of Volcher Coiter, of Johann Vesling, and possibly of Albrecht von Haller were known to the Japanese, and each is supposed to have contributed in some way to their understanding of Western anatomical knowledge and to have been "read" in connexion with the composing of the *Kaitai shinsho*. Perhaps it is not without some truth that the *Kaitai shinsho* has been referred to as the "Japanese Vesalius".

The men responsible for the composing of the *Kaitai shinsho* were the core of a group who believed in and fostered the learning in Japan of Dutch medicine and science. This small group was headed by Ranka or Ryōtaku MAENO (1723–1803) and Gempaku SUGITA (1732–1817), and upon the latter ultimately devolved the credit for the publication of the *Kaitai shinsho* in its final form. The unique importance of the *Kaitai shinsho* was, first, that it immediately overthrew and made obsolete the Chinese conceptions of human anatomy which had dominated the medicine of Japan for many centuries; second, that it caused a renaissance in *all* fields of Japanese learning and culture; and, third, that it directed attention to the accuracy and superiority of Western knowledge as exemplified by Dutch books.

Within a few years the *Kaitai shinsho* was revised by Bansui or Gentaku ŌTSUKI (1757–1827) in a manuscript composed in 1798 and published in 1812 with the title *Jūtei kaitai shinsho*. An accompanying atlas followed in 1826(?) and shows the influence of still another Western anatomy, Bartholomaeus Eustachius' *Tabulæ anatomicæ* . . ., probably from the Dutch text by Andr. Bonn (Amsterdam, 1798) or as revised by J. C. Krauss (Amsterdam, 1800), with the plates of Eustachius re-engraved by Bernard Siegfried Albinus and copied by another hand for these Dutch editions.

Western obstetrics seems to have first made its appearance in Japan by means of Hendrik van Deventer's *Dageraat der Vroededvrouvven* (Leyden, 1696) and/or his *Manuale Operation Zijnde een Nieuw Light* . . . (Leyden, 1734 or 1746), influencing the work of Genshu or Kakuryō or Motochika or Shinhō KATAKURA (1750–1822) who copied many of Deventer's plates in the *Sanka hatsumō* which was published in 1799. KATAKURA also copied William Smellie's obstetrical forceps, which had been figured in the Dutch translation by Matthys van der Haage, *Verzameling van Ontleedkundige Afbeeldingen* . . . (Amsterdam, 1765). Earlier, in 1773, some influence of Western obstetrics had been felt in Japan, since certain extracts from unspecified Dutch and English books were incorporated in the *Sanikuhen* by Bumpaku YAMANOBE. This work, however, appears not to have had as much influence among the Japanese as did the later writing of KATAKURA . . . Later on, the obstetrical books of Gottlieb Salomon, of Alfred Meadows, and of Karl Ludwig Ernst Schroeder were translated, in whole or in part, into Japanese.

Boku or Kōki or Shōshū MITANI (1774–1823) composed in 1802, and first published in 1813, a description of the whole system of human anatomy in a work entitled *Kaitai hatsumō*. That work was distinctive as the first *printed* Japanese anatomy to use colour wood-block illustrations; it was based partly on original Japanese dissections and partly on an exposition of "new Dutch theories" (of human anatomy), the Western sources not specified by MITANI.

The Western sources used by Genshin or Shinsai UDAGAWA in his work, the *Ihan teikō* (1805), with its magnificent copper-plate atlas separately titled *Ihan teikō-zu* or *Naishō dōhan-zu* (1808), are more certain. Dutch editions of the works of Stephen Blancard, his *De nieuw hervormde anatomie* . . . (Amsterdam, 1686) and/or his *Anatomia reformata* . . . (Lugd. Bat., 1687); of Jan or Jean Palfyn, his *Heelkonstige ontleeding van's menschen lighaam* . . . (Leyden, 1718 or 1733) and/or his *Waare en zeer naauwkeurige beschrijving der beenderen van's menschen ligchaam* . . . (Amsterdam, 1758); and an unidentified work of Jakob Benignus Winslow are known to have been used by UDAGAWA. The title-leaf of the *Naishō dōhan-zu*, shown in Fig. 4, is a re-engraving of Blancard's title page with a medallion portrait of Blancard *supra*. This anatomical atlas is distinctive as representing the first copper-plate engravings to be used in Japan to illustrate a medical work.

One or both of the Dutch editions of Palfyn's books on anatomy was the basis for a later translation into Japanese, by Isaburō NAKAYA in his work known as *Kaibō-zu* which was published in the fifth year of the Bunsei period (=1822). The title-leaf of the *Kaibō-zu*, and an illustration from it, appear here as Fig. 5. It is interesting to note that the Japanese text describes Jan or Jean Palfyn as a Belgian specialist in cancer who himself died from that disease.

It was Genshin or Shinsai UDAGAWA who began the first Japanese translation of a Western work on ophthalmology, from an unidentified Dutch edition (1787) of Joseph Jakob von Plenck's *Doctrina de morbis oculorum*. UDAGAWA's abridged translation was expanded by Kinchō or Rikkyō SUGITA (1786–1846), who published it in 1815 as the *Ganka shinsho*. Dutch ophthalmology was compared with the classical Chinese ophthalmology then still used in Japan, by Fuichi or Shinichi or Toshiatsu HONJŌ (died 1846) in his *Ganka kinnō* (1831) and in his *Zoku ganka kinnō* (1837).

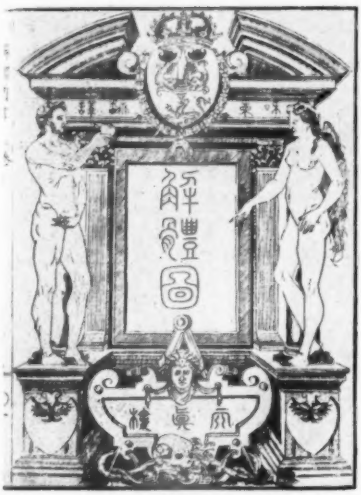


FIG. 3.—Title-leaf of the atlas of the *Kaitai shinsho* (1774).



FIG. 4.—Title-leaf of the *Ihan teikō-zu* or *Naishō dōhan-zu* (1808).



FIG. 5.—Title-leaf, and one of the anatomical plates of the *Kaibō-zu* (Bunsei period, 1818–1829). From *Meijizen Nippon igaku-shi*.

Most of the books by Joseph Jakob von Plenck appear to have been known in Japan, and the influence of his writings on Japanese medicine during the first third of the nineteenth century was great. The second edition in 1787 of Plenck's *Doctrina de morbis venereis* was, through the intermediary of a German translation by Franz Xaver August von Wasserburg and of the Dutch translation by Lambertus Nolst, *Verhandeling over de venusziekten* (Dordrecht, 1792), used by Kōgyū YOSHIO (1724–1800) to compose his work on syphilis, *Morenki baisō-ron* (n.d.). The Dutch translation was also used by Kinchō SUGITA in his *Baiso shinsho* (1820). Kinchō SUGITA wrote the first *complete* Japanese translation of a work on Western surgery in his *Yōka shinsen* (1830), which was based on Plenck's *Compendium institutionem chirurgicarum pro tironibus chirurgicae*. That same Western work was also used by Eihō YOSHIO (1785–1831) in his *Plenck geka-sho* (n.d.). The *Fujin byōron* (1850), a work on gynæcology by Takedō FUNABIKI or FUNANARI, was based on Plenck's *Doctrina de morbis sexus feminei*.

After the famous Japanese manuscripts and printed translations of parts of Paré, Western surgery made its greatest impact in Japan by means of a Dutch edition of Lorenz Heister's *Chirurgie*, identified as *Heelkundige onderwzingen* . . ., the second Dutch edition (Amsterdam, 1755). According to the account of this book as given in the *Rangaku kotohajime*, Gempaku



FIG. 6.—Illustration from the *Yōka seisen zukai* (1820).



FIG. 7.—The first Japanese stethoscope (1848). After NAGAYAMA.

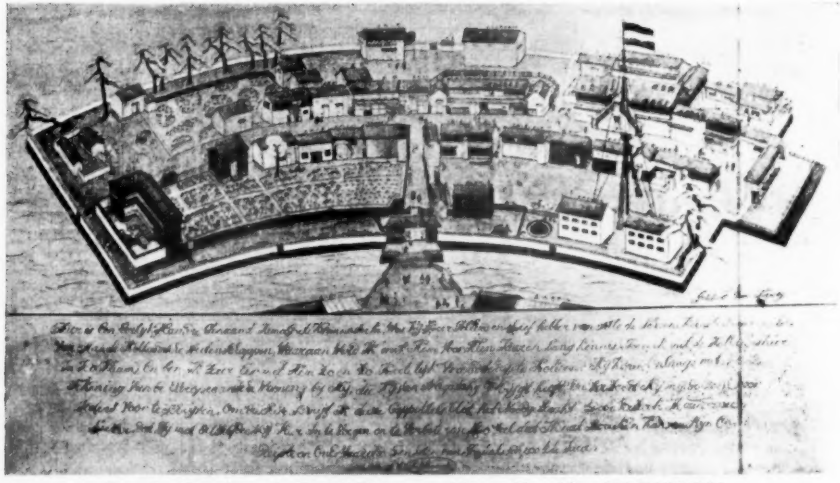


FIG. 8.—Deshima, the Dutch Factory at Nagasaki. After NAGAYAMA.

SUGITA borrowed it from Eishō or Kōgyū YOSHIO, who had traded 20 barrels of *sake* (rice wine) for the book which had been brought into Japan about the year 1767. SUGITA copied the illustrations, finished a translation of those parts of Heister concerned with bandaging, and started a translation apparently of the entire Dutch work. Bansui or Gentaku ŌTSUKI completed that translation in a manuscript dated 1792 known as the *Yōi shinsho*, some parts of which were later published. For example, Genkan ŌTSUKI, the son of Gentaku, revised that part of his father's work concerned with bandaging and in 1814 published the *Geka shūko* (sometimes referred to as *Taisei geka shūko*). Kōgyū YOSHIO also based at least his work on the treatment of wounds and bandaging, the *Kinsō-ron*, on Heister's book.

An independent translation of Lorenz Heister's *Heelkundige onderwzingen* . . . was made by Shinzō or Tokumoto KOSHIMURA in 1819 in an unpublished manuscript of 100 *hen* (=parts or volumes or books or sections or chapters). However, in 1820, KOSHIMURA

did publish a two-volume work entitled *Yōka seisen zukai*, illustrating various surgical operations and instruments—copied from Heister—with explanations and instructions. Fig. 6 is taken from a leaf of KOSHIMURA's atlas, showing an ophthalmic procedure with detail of the eye and some of the instruments used. The works of Tommaso Alghisi and of Ambroïse Paré, and perhaps also of François Tolet, are supposed to have contributed to KOSHIMURA's *Yōka seisen zukai*. It is not known, however, if that influence was directly from Dutch editions of their works (except for Alghisi, whose *Litotomia ovvero del cavar la pietra* appeared only in Italian editions) or indirectly through the intermediary of Heister who is known to have imitated the plates of those earlier writers. . . .

In the year 1818 an English book on Jennerian vaccination (possibly a copy of Jenner's *Inquiry . . .*) almost got into Japan, by being offered as a gift from a British sea captain to a Japanese physician to whom he had demonstrated the preparation of the smallpox vaccine. But the gift was refused, and fate was to decree that Western vaccination would be introduced to Japan by means of an obscure Russian writing, known in Japan by the title *Spop isbāwissha soueruseno wot was henoi saraza*[1] (St. Petersburg, 1803) which was translated into Japanese by Sadeyoshi or Sajūrō BABA (1786–1822) in a manuscript entitled *Tonka hiketsu* (1820), later to be published in 1850 with the title (*Wo*) *Roshia gyūtō zensho*. Opposed to this, however, is the generally accepted belief that Western vaccination first came into Japan with the arrival there in 1848 of Otto Theophil. Joh. Mohnike.

Philipp Franz von Siebold spent two separate periods in Japan, the first visit from 1823 to 1829 and the second visit from 1859 to 1861. His personal influence in the evolution of Japanese understanding of Western medicine in all of its varied aspects was perhaps greater than that of any other European who visited Japan. He was noted as a bibliophile and it is probable that he brought with him many Western works on medicine and surgery. Soon after his first visit Japanese translations of Western authors began to appear in ever-increasing numbers. We will content ourselves here with calling attention only to the most outstanding of such writings. In 1832 Kōan OGATA (1810–1863) wrote a work known by various titles, most commonly as *Jinshin kyūri shōkai* or as *Rasetsu jinshin kyūri*, which had been derived from the *Handboek der natuurkunde van den mensch* of Theodorus Georgius Augustus Roose and from the Dutch translation by Adolphus Ypey, *Handleiding tot de phijsiologie . . .* (Amsterdam, 1809) of Roose's *Handbuch der Physiologie des Menschen*. The publication in printed form of this work by OGATA is very much in doubt. The works of Roose, and of Johann Friedrich Blumenbach in Dutch translation, *Grondbeginselen der natuurkunde van den mensch* (Amsterdam, 1835), were also used later by Chōei TAKANO (1804–1850) when he composed the *Igen sūyō* and published it in 1836. This translation by TAKANO is generally regarded as having been the first physiological writing in Japan to be based on Western books.

The work of Christoph Wilhelm Hufeland, from the Dutch translation by H. H. Hageman, *Enchiridion medicum. Handleiding tot de geneeskündige praktijk . . .* (Amsterdam, 1838), proved to be very influential in Japan. Kōan OGATA translated the "Praxis" into Japanese in his book *Hushi kēikun ikun* which was published in 1843. Various other parts of Hufeland's book were also translated by Bairi or Seikai or Seikyō SUGITA (1817–1859) in his *Saisei sampō* (n.d.) and in his *I-kai* (n.d.). These Japanese translations were widely read. Except for only two earlier attempts by the Japanese to elucidate the philosophical aspects of human pathology, the *Byōgaku tsūron* by Kōan OGATA is regarded as the first Japanese writing on general pathology. It appeared in 1847 or 1849 and consisted, for the most part, of translated abstracts from the published works of Christian Wilhelm Hufeland, of Georg Wilhelm Christoph Consbruch, of Johann Wilhelm Heinrich Conradi, of Philipp Carl Hartmann, and of Kurt Polykarp Joachim Sprengel. Except for the Dutch edition of Hufeland's work, noted above, none of the Western original books used by OGATA is known.

Anthelme-Balthasar Richerand's *Nouveaux élèments de physiologie*, in the Dutch translation by A. van Erpecum, *Nieuw grondbeginselen der natuurkunde van den mensch* (Amsterdam, 1826), attracted the attention of several Japanese physicians. It was translated in 1844 as the *Iri-gaku gen* by Sodō HORIUCHI (1801–1854), Ryōan KUROKAWA and Kenzō AOKI; and in 1855 as the *Jinshin kyūri sho* by Genkyō HIROSE (1821–1870); and by Gempo MITSUKURI (1799–1863) in his *Jinsei kyōgen* (n.d.).

An interesting situation is presented by a Scottish (?) missionary-physician, Benjamin Hobson, who went to China in 1839 and spent the next twenty years in practice—and, with the help of a Chinese physician, CHIN Shū-dō, in the translation of European medical books into the Chinese language. One such collection of summaries or abstracts was further translated from Chinese into Japanese by CHIN, and in 1857 was published in Japan the remarkable work known as the *Zentai shinron*. The *Zentai shinron* contained extracts from several

[1]Transliterations into the Roman alphabet are not always easy, and this title may, more correctly, be *Sposob isbāvitsia sara (—) eniia ot (ospa) gnoinoi sarasai.*

Western medical books, notably English editions—for example, William Cheselden's *Anatomical tables . . .*—and this Japanese translation was destined to introduce much of Western medicine to the island empire.

An epidemic of cholera had ravaged parts of Japan in 1821–22, evidently for the first time, but the second epidemic in 1858 precipitated the first Japanese work on the subject—a book entitled *Korera byōron*, by Ryōkaku SHINGŪ, Ryōmin SHINGŪ and Tatsukichi OMURA. That work was, for the most part, a translation of an unidentified book on cholera which had been written by Georg Friedrich Most.

Medical instrumentation of the Western world was introduced into Japan by: microscopes (*c.* 1787), clinical thermometers (*c.* 1826), and stethoscopes (1848) which had been brought in by European physicians; models which were promptly imitated by the Japanese. The first Japanese stethoscope was made in wood by Eikyū or Umejirō SHINAGAWA (1808–1857), and is shown here as Fig. 7. This original model is—or was—preserved in the Nagasaki Medical College.

Nagasaki was the place in Japan through which most of the contacts with the Western world were made, by means of the Dutch Factory at Deshima. Fig. 8 is a reproduction showing the plan of Deshima from an old print. It was on a rock at a beach near Nagasaki that Jacobus L. C. Pompe van Meerdervoort, a Dutch physician and anatomist, performed, on June 9, 1859, the first dissection of a human body done by a Western person in Japan. Afterward, Pompe van Meerdervoort established several hospitals and popularized autopsies for teaching purposes.

This brief account of the principal Western influences in the development of pre-Meiji Japanese medicine, more especially from the bibliographic aspects, ends with the beginnings in 1857 of the present medical school of the University of Tōkyō. The Edo or Tokugawa period itself ended in 1867 with the overthrow of the Shōgunate and the "restoration" of the Emperor Meiji, and thus began the modern period in Japan.

Of equal interest is how knowledge of early Japanese medicine came to the Western world. Except for possible oral descriptions carried back to Europe by returning missionaries and physicians, the principal means were the writings of Willem ten Rhyne and of Engelbert Kaempfer. ten Rhyne's *Dissertatio de arthritide: mantissa schematica: de acupuncturа . . .* (London, 1683) was the first such writing. ten Rhyne followed that up with another account entitled "Der Chinesen und Japaner Weise, wie selbige allerley Kranckheiten durch das Brennen mit der Moxa, und Stechen einer gulden Nadel, völlig und gewiss curiren," which was obscured or even "lost" by being incorporated *in* Stephen Blankaart's *Accurate Abhandlung von dem Podagra . . .* (Leipzig, 1690). This title is sometimes given as *Verhandeling van het podagra en vliegende jigt*. Kaempfer's *Amoenitatum exoticarum politico-physico-medicarum, Fasciculi V. . .* (Lemgoviae, 1712) had the advantage of being a separate publication, and became even better known than ten Rhyne's earlier descriptions. Willem ten Rhyne (in Japan from 1674–77) and Engelbert Kaempfer (in Japan from 1690–92) were, then, the first to report to the West on early Japanese medicine. Except for Kaempfer's famous *History of Japan* (London, 1728), there were no descriptive writings by Western physicians for about one hundred years; not, indeed, until the time of Karl Peter Thunberg, who gave much information in his *Voyages de C. P. Thunberg, au Japon . . .* (Paris, 1796). Later on, Philipp Franz von Siebold gave some of the best accounts of the time in a series of publications beginning in 1824 and culminating in his *Nippon. Archiv zur Beschreibung von Japan . . .* (Leiden, 1832–52, 7 vols. 2nd edition, Wurzburg und Leipzig, 1897, 2 vols. New edition, Berlin, 1930–31, 3 vols.).

Since this paper is only an introduction to the subject and not an exhaustive account, a list of "selected references" is appended, chosen by the writer as giving the most useful information for an understanding of Western medical influences in Japan in pre-Meiji times.

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Worms in History with Special Reference to Children

By JOHN RENDLE-SHORT, M.D., M.R.C.P., D.C.H.

Department of Child Health, University of Sheffield

IN the old London Bills of Mortality and in books on children's diseases in past centuries, three conditions recur again and again—teething, convulsions and worms. I have considered the first two of these in previous communications (Rendle-Short, 1955*a*, *b*). The present paper deals with the subject of worms.

There are probably three main reasons for the concept that worms cause disease. Firstly, as Grattan and Singer (1952, p. 99) wrote with regard to Anglo-Saxon medicine, "There is a constant association of ideas between the poison of the serpent and the supposed venom of the worm".

Secondly the presence of worms or maggots in a body after death has been known from antiquity. Meat left too long soon harbours maggots, and it was commonly supposed that they entered the body while the animal was still alive. Andry (1701, p. 24) mentioned that some people thought that if meat was kept in stoppered bottles protected from flies, maggots would not develop. He, however, rejected this idea without apparently trying the experiment himself. From the dead body with its grubs to the living body with its worms is obviously only a small step.

The third reason for the concept of the evils of worms is that they were so frequently found in sick people. Failing any other obvious cause for an illness, worms were apt to be incriminated.

In ancient oriental medicine worms figure prominently. From the Vedic period (1500–900 B.C.) we have the Atharva-Veda Samhita. In this there are incantations against worms.

> "O Indra, lord of riches, smite thou the worms of this boy; smitten are all niggards by thy formidable spell.
> "What one creeps about his eyes, what one creeps about his nostrils, what one goes to the midst of his teeth—that worm we grind up.
> "The worms that are white-sided, that are black with white arms, and whatever ones are of all forms—these worms we grind up" (Whitney, 1905).

Hippocrates (*c.* 440 B.C.) described worm infestation in some detail. He claimed that worms were formed while the child was still *in utero*. He advanced two arguments in support of his theory: Firstly that fæces never remain in the bowel long enough for an

animal of such size to be formed. It could not be produced even if there was no action of the bowel for several days. Secondly that when given a purge immediately after birth, children often passed a roundworm or a tapeworm with the first stool.

Chronologically far later, we come to the Anglo-Saxon period (around A.D. 1000) when medicine was a mixture of pagan magic and Christian teaching. According to Grattan and Singer (1952, p. 99), "There is hardly a symptom from toothache to fits that is not at one time or other ascribed to worms". In the Lacnunga, an Anglo-Saxon magico-medical common-place book dated around A.D. 1000 there is this spell:

> *In case a man or beast swallow a worm.*
>
> If it be of male kind sing this lay which is written hereafter into the right ear; if it be of female kind sing into the left ear" (Grattan and Singer, p. 107).

The spell itself was gibberish and unintelligible. It had to be sung nine times into the appropriate ear and then a single Paternoster. No instructions were given as to how the ingested worm should be sexed.

But to come down to more recent times. At the beginning of the eighteenth century Nicholas Andry produced his "Account of the breeding of worms in human bodies" (1701). According to him almost every ill was due to worms, so much so that he earned the nickname "Homo vermiculosus" (Still, 1931). He considered that all living creatures had their worms: vegetables, wood, coral, oysters, shell-fish, liver of sheep and "there is scarce any fish without them". Human worms he divided into two main types: those in the gut and those outside it. The latter included worms bred in the ears, teeth, lungs, liver and heart. (These could be seen in blood-letting and from the description may have been blood clots.) In addition there were "vesicular" worms (Plate I, Fig. 5), worms from sores

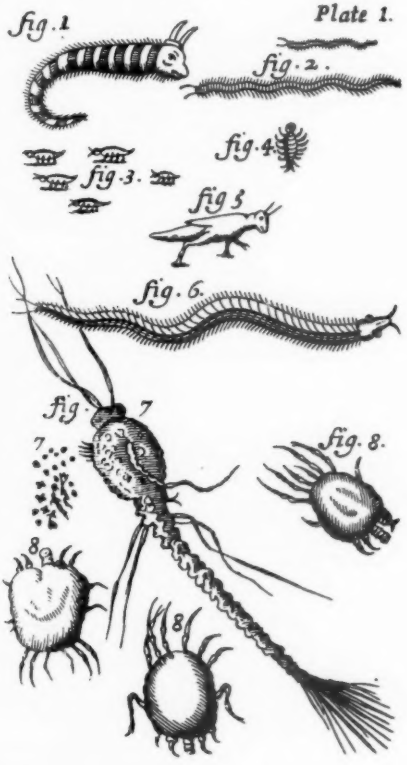


PLATE I.—Reproduced from Andry (1701).

and gangrene (Plate I, Fig. 6) and cutaneous worms (Plate I, Fig. 7) which appeared on the arms and legs and especially on the backs of breast-fed children. He acknowledged that some people considered these to be hairs not worms. Perhaps he was thinking of lanugo hairs, or more probably of blackheads. Ettmüller (1676) described a treatment for these worms which, "skulk under the skin especially about muscular places". The child was to be bathed in warm water in which chickens' dung had been boiled and then rubbed all over with honey to tempt the worms to come out in the form of black hairs. These could then be scraped off with a crust of bread "made sharp like the edge of a knife".

"Wax worms (Plate I, Fig. 8) lived under the skin creeping about and producing blisters which "occasion a vehement itching". It was possible to discover this worm when the blister was pricked. These worms, presumably *Sarcoptes scabiei*, were called "wax worms", "because stale wax is most apt to be eaten by them".

Andry (1701, p. 55) also mentioned umbilical worms which "breed in the navel of children and give 'em a great deal of trouble. They make 'em very lean and throw 'em into Universal Decay". He continued: "There is no other sign of this worm but this that if you fasten a gudgeon on the navel, next day part of the fish will be corroded." The gudgeon (Oxford English Dictionary) is a small fresh water fish which is easily caught. The word is now used to describe a person who is easily deluded. Perhaps Andry did not know this.

Ettmüller (1676), too, mentioned the umbilical worm and suggested treating the affliction by applying the gudgeon to the belly for a few nights and then substituting, "the inner shell of a walnut filled with powder of venice glass". Presumably the worm enjoyed eating the fish and returned for more, only to eat the glass by mistake and die.

Most authors described only four varieties of worm:

Old Name	Modern Name
Round and Short: Ascarides	*Enterobius* (or *Oxyuris*) *vermicularis;* threadworm; pinworm; seatworm
Round and long	*Ascaris lumbricoides;* roundworm
Flat and long; Tænia ..	*Tænia solium* (or perhaps *saginata*); tapeworm
Flat and short	Isolated proglottides of tænia

Bracken (1737), however, described three types: roundworms, broad worms and horrid worms. The latter had many feet, two heads and some a double forked tail.

We will now consider threadworms, tapeworms and roundworms in greater detail.

Threadworms.—Astruc (1746) wrote that ascarides caused the patient to feel "a troublesome sensation in the fundament", and Bracken (1737) described small worms which live "about the sphincter muscle of the anus". Armstrong (1777) mentioned that threadworms usually only appeared after the infant had been weaned, but occasionally they were seen in breast-fed babies if the mother had been subject to the same type of worm from infancy.

Specific treatment for threadworms was not often described but Rosen von Rosenstein (1776) suggested several forms of therapy, the most notable of which was a clyster (enema) of rats' dung and sugar in tepid milk to be administered six nights running. Alternatively, a clyster of tobacco smoke could be given. Another ingenious treatment he suggested was to tie a string to a piece of fresh pork which was then inserted into the rectum. The worms apparently bit the pork and could thus be removed. The pork had to be changed and the fishing continued for some time in order to evacuate all the worms.

Tapeworms.—As might be expected most descriptions of tapeworm infestation concern adults. However, Harris (1689) described the 3½-year-old daughter of an Earl (many of Harris's case histories refer to titled children) who had a slow fever, was sleepy and had twitching of the nerves and a dry cough. She was given clysters, purges and emetics for six days, which caused her to pass a worm "a span long, after which she was presently relieved from her whole disorder". Brouzet (1755) described flat-worm infection in older children who had continual spitting, paleness, weakness, pains in the liver and offensive breath. Slimy stools occurred in which small pieces of the worm were voided. He mentioned an irregular appetite, but Rosen von Rosenstein (1776) described a state of continual hunger and recorded that a woman who later passed 18 tapeworms, ate voraciously day and night.

The treatment of tapeworm infestation was long and arduous and consisted chiefly in starvation and purgatives. Sometimes worms lived to a great age—15 years is recorded.

Roundworms.—At the present time in this country these helminths are infrequent and

innocuous, but this was not so in the past, and even to-day in some parts of the world they are common and dangerous. The difference lies partly in the poor nutritional state of the victims—itself to some extent the result of the roundworms—but mainly because of the large number of infesting worms. de Silva (1956) records that in Ceylon the passage of 100–200 or even up to 1,000 worms is not uncommon.

Ascaris lumbricoides has only one host—man. The clue to the problem of worm infestation therefore lies in the method of disposal of fæces. This in the past was very casual. Norman castles had their garderobes placed in a corner with a wooden seat and a stone shaft which discharged at the base of the wall or into the moat (Quennell and Quennell, 1947). In 1596 Sir John Harrington, a poet and godson of Queen Elizabeth, invented the first water closet. In the pamphlet in which he described his invention, he gave a long account of the state of affairs which then existed. He wrote "Even in the goodliest and statliest palaces of this realme, notwithstanding all our provision of vaults, of sluces, of grates, of poore folkes in sweeping and scouring, yet still this same whorsom sourie stink though he were commanded on pain of death not to come within the gates yet would spite of our noses even prease to the faire ladies chamber."

But Harrington's closet did not become popular, and indeed it could not be of any great value until the introduction of main drainage which only occurred in London in 1865. Meanwhile in towns, privies were usually just a single bucket at the bottom of the stairs, and the newer part of London was built over cesspools. According to Creighton (1894) the soil of London "was full of organic impurities including the decomposition of many generations of the dead. A hot summer raised an effluvia from the ground such as the modern residents have no experience of". Parson Woodforde (1799) was probably as well situated as anyone in his day with his "Jericho" as he called it. This consisted of a seat in the garden which discharged directly into a pit which projected at the back so that it could be emptied. This refuse would then have to be disposed of, probably by strewing it on the land. Obviously there was ample opportunity for the contamination of food.

Most later writers believed that worms came from eggs. Some remarked that they did not know where the eggs came from (Brouzet, 1755; Astruc, 1746). Ettmüller (1676) incriminated corn or bread, but the majority of writers believed that fruit and vegetables were the offending articles of diet (Pechet, 1697; Boerhaave, *c.* 1724; Underwood, 1784). It was for this reason that these foods were usually forbidden to children, which may have saved them from worms, but almost certainly resulted in their contracting scurvy. One of the few writers who was willing to brave the dangers of fruit eating was Cadogan (1748), who wrote: "Some may think they (fruit and vegetables) carry into the stomach the eggs of future worms; but of this I am not very apprehensive: for I believe there are few things we eat or drink that do not convey them."

The signs and symptoms of roundworm infestation can be divided into medical and surgical. Many writers describe the former. Thus Pechet (1697) listed: a mouth full of spittle, teeth grinding, dreams, scratching the nose, chewing, dry cough, nausea, vomiting, "kickops", thirst, swollen belly, cold sweats, flushing, fits and fevers. Tissot (1765) gave a similar list but added that the belly was "larger than ordinary, the rest of the body meagre". He also included palsies of hands, arms or legs, "gums in bad state as though gnawed or corrupted and even loss of sight or speech". Andry (1701, p. 90) described the case of a "young girl that was dumb eight days and recovered her speech after she had voided 40 worms by stool". Plate II shows a roundworm illustrated by Andry.

fig. 11



PLATE II.—Reproduced from Andry (1701).

The mention of fever is interesting. It was the frequent appearance of worms in fever-ridden patients which led to the idea that the worms caused the fever. Harris (1689) went so far as to write a section in his book entitled, "Of worms producing the smallpox" and

gave a case record. Butter in 1782 published "A treatise on the infantile remittent fever", which he said is, "Commonly but very unjustly called the worm-fever". He continued, "the patients generally pass worms in the course of this fever even when they were never known to void any before".

Surgical ascariasis is virtually unknown in this country to-day, but in those parts of the world where the standard of hygiene is low, the condition occurs quite frequently. In 1955, 53 cases of partial and 10 cases of complete intestinal obstruction, and 10 cases of acute peritonitis all due to surgical ascariasis were admitted to the Surgical Unit of Colombo Children's Hospital (de Silva, 1956). In times past, owing to heavy infestation and the frequent use of violent purges and vermifuges surgical complications were common.

Many old writers considered that worms could obstruct the gut and compress and irritate the bowel (Tissot, 1765). They also caused trouble by gnawing them (Boerhaave, *c.* 1724). Pechet (1697) wrote that, "white worms are better than yellow, livid red or blackish". They were better evacuated by stool than upwards, "and worst of all when they eat their way out". Andry (1701, p. 92) described the case of a young man of 15 who was very sick. He was made to take "a certain powder" which "caused him to void downward above 100 worms. But after all the belly continuing hard and stretched toward the navel (a plaster was applied) and twenty-four hours after several worms of good length began to come out from his navel". Later the lad ate some strawberries and "the grains or seeds" also came out. Andry concluded, "this will not permit us to question but that the bowels and the containing parts were pierced by the worms". Presumably the lad had intestinal obstruction with perforation of the gut and peritonitis which discharged through the umbilicus.

The most famous case of intestinal obstruction associated with worm infestation was that of Herod Agrippa. St. Luke tells us (Acts, xii, 22) that after the King had made an oration, the people, wishing to curry favour with him, cried out that it was the voice of a god not a man. "Immediately an angel of the Lord smote him, because he did not give God the glory; and he was eaten of worms and died." From Josephus (*c.* 93) we can learn more about the same incident. He tells us that after the shout of the people, the King did not "rebuke them, nor reject their impious flattery". But he looked up and "saw an owl sitting on a certain rope over his head, and immediately understood that this bird was the messenger of evil tidings, and fell into the deepest sorrow. A severe pain also arose in his belly and began in a most violent manner". Herod lingered on, the pain becoming more severe for five days, and then he died. Josephus did not mention the worms nor St. Luke the pain, but putting the two accounts together we almost certainly have a case of acute intestinal obstruction with perforation of the intestine and death caused by, or in association with, worms.

Returning to more recent times, a few writers even in the eighteenth century rejected the theory that worms pierced the gut. Brouzet (1755) remarked that even though he had seen worms and fæcal matter spread over the intestine, he considered it was caused by "the inflammatory and gangrenous contractions and twisting of the gut", not by the worms.

Treatment

Irrespective of their views on ætiology or symptomatology, all writers had definite views on the treatment of roundworms. These consisted mainly of purges. Calomel (Bracken, 1737), or syrup of wormwood, rhubarb or senna (Harris, 1689) was prescribed. Underwood (1784) suggested pewter filings and treacle, "of which children of 4–5 years old may take several teaspoonfuls in a day almost at pleasure". This treatment probably killed both worms and children by lead poisoning. Naturally enemas were not neglected. Pechet (1697) suggested giving the child bitter things to take by mouth. This was to drive the worms into the lower gut. Sweet things were then injected as an enema to tempt them farther down. The same method was advised by Astruc (1746), but after attracting the worms with a sweet enema he advised a bitter one to kill them. He wrote with evident glee, "I like very much this practice".

Rosen von Rosenstein (1776) gave various rules for ridding a child of roundworms. Any medicine, he wrote, must be swallowed at the time the patient would normally be having breakfast, for as "worms are accustomed to feed at that time, one may more easily cause them to suck or feed on that which is given to kill them". It was most important that the remedy be attempted only when the moon was waning. Lastly he advised that the patient must not be allowed to smell the medicine before it was given as then the worms would hide.

Teething, convulsions, and worms; these three were regarded as the great diseases of children before the advent of scientific medicine. Of the trio worm infestation was certainly not the least important.

Summary.—The concept that worms cause disease goes back to antiquity. It probably arose partly from fear of serpents, partly because maggots could be found in dead or putrefying material and partly because worms were known to inhabit the gut of man and animals.

Owing to poor sanitation worm infestation was far commoner in the past than it is in civilized communities to-day. Many medical symptoms including fevers were ascribed to ascariasis in children. Intestinal obstruction with perforation was not uncommon when large numbers of worms were present. Treatment was crude, it consisted mainly of bitters to drive the worms to the lower intestine, or sometimes sweet enemas to encourage them there. It was hoped that they would then be easily voided.

Acknowledgments.—I would like to thank the librarians of the following libraries for their unfailing help: The Royal College of Physicians, The Royal Society of Medicine, The University of Sheffield and the Wellcome Historical Medical Library. Finally, my thanks are due to Professor R. S. Illingworth for his kindly criticism.

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Section of Dermatology

President—Louis Forman, M.D., F.R.C.P.

[*May* 16, 1957]

Papulonecrotic Tuberculides with Miliary Tuberculosis.—I. S. Hodgson-Jones, M.D., M.R.C.P.

Mrs. E. M. F., aged 49. Three years ago this patient had a severe pyrexial illness which was not diagnosed. Eighteen months ago she started to develop crops of papules on her legs, which, having broken down centrally, were very slow to heal and left scars. These have been recurring ever since and have become worse lately.

Apart from a slight cough in recent weeks, her general health has been good. General physical examination revealed no abnormality except the necrotic and scarred lesions on her legs which appeared to be papulonecrotic tuberculides.

Investigations.—X-ray of the chest revealed a fine reticular mottling throughout the whole of both lung fields, with a diffuse hilar flare but without obvious glandular enlargement, which was thought to be miliary tuberculosis. X-ray of the abdomen showed no calcified glands. The blood picture and erythrocyte sedimentation rate were normal, as were the plasma protein estimation and the cerebrospinal fluid. Biopsy of a skin lesion taken from the leg showed central caseation with a surrounding tuberculous reaction. No tubercle bacilli were found in the sputum or in gastric washings. The Mantoux test was negative 1 : 10,000 but positive 1 : 1,000.

Treatment.—Following bed rest, together with streptomycin 1 gram i.m., PAS 15 grams, and prednisolone 15 mg. daily, the lung lesions cleared up in six weeks and no new tuberculides have appeared on the legs.

Comment.—Opinion has been divided as to the nature of the changes in the lung fields, particularly as to whether they are early or late miliary tuberculosis. The patient's relatively good health, normal erythrocyte sedimentation rate and the long history of lesions on the legs, make one feel that this might be chronic healed miliary tuberculosis, as described by Hoyle and Vaisey (1937, Chronic Miliary Tuberculosis, London), the original dissemination having taken place three years ago when she had her severe pyrexial illness. Against this, however, is the fact that no calcification has taken place, and the response to antitubercular therapy has been rapid, indicating perhaps, changes of a more recent origin.

Dr. B. C. Tate: I wonder if Dr. Hodgson-Jones looked for tubercle bacilli in the sections?

Dr. Hodgson-Jones: No, we did not look for bacilli in the sections because one so seldom finds them in papulonecrotic tuberculides. They were looked for in the sputum and gastric washings but were not found.

Dr. C. H. Whittle: One can have a completely silent tuberculosis which is both active and widespread. I once saw a hernial sac, removed from a boy aged 4, which was studded with tubercles in which were found acid-fast bacilli and the histology showed miliary tuberculosis. The patient was perfectly well, but similar tubercles were present and were felt by the surgeon's finger over the abdominal peritoneal surface.

Incontinentia Pigmenti.—W. Frain-Bell, M.D., M.R.C.P.Ed. (for R. T. Brain, M.D.).

E. B., female, aged 5 months.

History.—This child was born on 19.12.56 as a full-term normal delivery, birth-weight 5 lb. 8 oz. On the first day of life reddish marks appeared on the skin of the forehead and scalp, similar lesions being noticed the following day on the arms and legs. Blisters were seen for the first time on the third day and recurrent extensive blister formation continued until the age of 9 weeks, when they gradually reduced in number, hyperkeratosis forming at the sites of the blisters associated with development of dark brown pigmentation, which was linear in some areas. During the last six weeks the hyperkeratotic areas have gradually cleared, the main abnormality now being the residual pigmentation. The child's progress since birth has been normal, except for retarded weight gain during the early months; the parents are not related and there is no history of other familial abnormalities.

On examination.—There is a widespread greyish-brown pigmentation, linear in arrangement in some areas, involving extensive areas of the skin of all parts of the body. There is in addition some residual hyperkeratosis on the fingers and left lower leg.

Dr. Henry Haber: Asboe-Hansen (1953) described 4 cases of bullous keratogenous and pigmentary dermatitis with blood eosinophilia in newborn girls. All 4 cases had severe eosinophilia combined with an acute eruption of papules, vesicles, bullæ and pustules localized on the limbs. In all cases the lesions healed with formation of thick warty keratoses, which on subsiding left scars and pigmentation. The pigmentation was not slate grey and showed more the character of ordinary pigmentation and not the pattern seen in Bloch-Sulzberger syndrome. Other ectodermal defects were absent. I have seen a similar case recently shown to me by Dr. T. Morgan. I wonder whether the case shown to-day does not belong to this group.

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Necrobiosis Lipoidica Diabeticorum and Granuloma Annulare.—W. FRAIN-BELL, M.D., M.R.C.P.Ed.

C. T., female, aged 16 years.

History.—This girl has suffered from diabetes mellitus for the last three years, which is at the moment reasonably well controlled with 65 units of NPH insulin daily and a diet of 1,800 calories; her maternal uncle also suffers from diabetes. Except for the skin lesions the diabetes is otherwise uncomplicated. Three years ago, a nodular eruption was noticed on the dorsum of the left foot; a biopsy was carried out but no firm diagnosis was arrived at. She was first seen by us in February 1956 and at that time she presented with grouped subcutaneous nodules on the dorsum of the left foot and ankle, some of which were noticed to be coloured; the clinical picture was that of granuloma annulare which was subsequently confirmed histologically. One month later a few fresh nodules were noted on the skin of both lower legs. She did not attend again until a year later (February 1957) at which time it was noticed that she had a number of reddish nodules on the front of the right leg and a few similar lesions on the left leg, the original nodules on the dorsum of the left foot being much smaller. In addition she had developed a plaque on the outer aspect of the left lower leg with a well-defined pigmented edge and a yellowish centre and telangiectasia, suggestive of necrobiosis lipoidica which was subsequently confirmed histologically. Further regression of the granuloma annulare lesions on the dorsum of the foot has occurred during the last six weeks.

On examination.—There are a number of firm reddish nodules on the front of both lower legs, more on the right side than on the left. There appears to be also some central scarring. One or two skin-coloured palpable nodules are still present on the dorsum of the left foot with thickening of the biopsy scar. On the outer aspect of the left leg above the ankle there is a firm well-defined plaque with a brownish periphery and yellow centre with telangiectasia.

Investigations.—Serum cholesterol 250 mg.%, lipids 1,300 mg.% (fasting normal 400–800 mg.%).

Histology (Dr. H. Haber).—23.11.56: There is one focus of change within the corium showing partial degeneration of collagen permeated by typical histiocytes and giving it a characteristic picture. Diagnosis: Granuloma annulare.

29.4.57: The epidermis does not show any diagnostic changes. The corium exhibits widespread areas of collagenous change exemplified by broadening and homogenization of their bundles. The inflammatory reaction envelops blood vessels and seems also to penetrate the tissue spaces of the collagen. Diagnosis: Necrobiosis lipoidica.

Comment.—From time to time it has been suggested that granuloma annulare and necrobiosis lipoidica may be variants of the same disease, especially as all the clinical, histological and histochemical findings in necrobiosis lipoidica have at times been associated with granuloma annulare. This existence of common features may be significant despite the ease of differentiation between classical examples of each condition. In this patient, it may be that the collagen change has been modified by the associated diabetic condition into giving rise to two extremes of the same basic condition, granuloma annulare on the one hand and necrobiosis lipoidica on the other.

The following cases were also shown:

Pemphigoid with Features of Dystrophic Epidermolysis Bullosa.—Dr. C. H. WHITTLE, Dr. J. A. LEAHY and Dr. R. A. DAVIS.

Rodent Ulcer Successfully Treated by Local Injections and Ointment Containing Colcemid.—Dr. N. A. THORNE.

Sarcoidosis.—Dr. R. J. CAIRNS.

(1) **Prurigo Ferox.** (2) **Hidradenome Eruptif.**—Dr. C. D. CALNAN.

Exudative Discoid and Lichenoid Chronic Dermatosis of Sulzberger and Garbe.—Dr. D. C. G. BETT (for Dr. G. C. WELLS).

Widespread Nævus with ? Ulerythema Ophryogenes.—Dr. P. R. MONTGOMERY (for Dr. LOUIS FORMAN).

Behcet's Syndrome.—Dr. I. J. MERENLENDER.

A short paper was read by Dr. V. WILSON on **A Case of Severe Leukopenia due to Amodiaquin Successfully Treated with Prednisolone.**

[*June* 20, 1957]

Macular Atrophy of the Skin.—R. G. HOWELL, M.R.C.P.

B. F., girl, aged 14 years.

History.—For thirteen months she had been developing lesions scattered on the trunk and legs. These begin as small, red, non-scaly papules which gradually heal at the centre, producing a dead white scar with slightly raised erythematous edge. Later the edge disappears.

On examination.—General health good. No serious illness in the past. Mild ichthyosis and keratosis pilaris. No adenopathy. Liver and spleen not palpable. C.V.S., abdomen and C.N.S. normal. Blood pressure 110/80.

Investigations.—Mantoux 1 : 10,000 positive. W.R. and Kahn negative. Hb 94% (14·4 g./100 ml.), W.B.C. 8,000 (polys. 44%, eosinos. 2%, lymphos. 50%, monos. 4%). E.S.R. 2 mm. in one hour (Westergren). Urine normal.

Histology (Dr. H. Haber).—The centre of the lesion shows marked atrophy of the epidermis, and there is a marked perivascular and periacinous lymphocytic infiltration in the dermis.

Comment.—The macular atrophic lesions in this case do not resemble the anetoderma of Jadassohn or the similar condition described by Schweninger and Buzzi in which the atrophic areas are flaccid and can be herniated on pressure. The clinical appearance in this case is similar to that described by Degos (1954) under the title "Papulose Atrophiante Maligne". This condition eventually involves the gastro-intestinal tract causing hæmorrhage and perforation. However, the histological picture described by Degos shows thromboses of vessels and necrosis without cellular reaction in the dermis. In a recent case described by Ingram and Sutherland (1957) the lesions were also necrotic.

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Ehlers-Danlos Syndrome.—E. WILSON JONES, M.R.C.P. (for H. J. WALLACE, F.R.C.P.).

Mrs. S. M., aged 19, gave a history that she had shown excessive liability to bruising from early childhood. In addition, cuts or abrasions tended to heal very slowly, leaving abnormal scars.

There was no family history suggestive of the Ehlers-Danlos syndrome. The parents and five siblings were stated to have a normal skin. It was, however, not possible to confirm this since our patient lives away from home.

On examination.—The patient was thin and looked generally undernourished. The striking abnormality of the skin was the presence of mottled pigmented scars over both knees and down the greater extent of both tibia. There were similar smaller scars over the points of both elbows. In parts the scars were baggy and papyraceous. Her skin was thin, but in no part demonstrated hyperelasticity. Her hands showed a mild degree of arachnodactyly. No hyperextensibility of the joints was found.

On general medical examination, the only other feature of note was the presence of faintly bluish sclerotics and on examining the heart a soft systolic murmur was heard in the pulmonary area without any other abnormal cardiac signs.

Investigations.—Plasma calcium 9·4, phosphorus 4·6 mg./100 ml. Clotting and bleeding time normal. Chest X-ray normal. Hb 70%, W.B.C. 7,400. Normal differential count. Platelets 494,000. Hess test negative. Electrocardiogram: Clockwise rotation, otherwise physiological.

Ehlers-Danlos Syndrome, with Spondylolisthesis and Malformation of the Terminal Digit.—LOUIS FORMAN, M.D., F.R.C.P.

Miss A. P., aged 23.

Family history.—Only child; her mother and maternal grandmother had abnormal elasticity of skin.

History.—Since birth there has been abnormal mobility of all joints and her skin bruised easily. At the age of 8, following an injury to the right leg, an ulcer developed which healed after a considerable period of time. It relapsed after another injury and again healed slowly. This sequence has been repeated. The present ulcer has been present for two years and attempts at suturing following excision have failed. Eighteen months ago some of her finger nails became yellow and flat, and the distal phalanges shortened.

Present status.—The skin is of fine texture, smooth and supple. It is hyperelastic over the cheeks, the neck and backs of the hands. Over the right shin there is a clean superficial ulcer 1¼ in. × 1 in. There is increased range of movement of all the limb joints, bilateral pes cavus and marked lumbosacral deformity. Five of the finger nails are flat, spooned, longitudinally striated.

Investigations.—Normal blood picture, normal proteins and serum calcium, normal clotting mechanism. Hess test negative.

X-rays: (1) Lumbosacral region: gross spondylolisthesis at the L.5–S.1 level.

(2) Numerous areas of subcutaneous calcification anterior to lower half of each tibia.

(3) The terminal phalanges of the 1st, 2nd and 5th fingers of the left hand and the 2nd finger of the right are malformed. Some show absence of the distal part of the phalanx. The intracapsular rim of bone is retained.

"The above findings are consistent with the findings in Ehlers-Danlos syndrome" (Dr. P. J. Hurley).

Skin biopsy.—From abdomen, connective tissue thin loose poorly-formed and poorly-stained bundles.

Elastic tissue, increased, thick and coiled.

Comment.—The two characteristic signs of Ehlers-Danlos syndrome are exhibited to some degree in this patient:

(1) Increased elasticity of the skin due to greater content of fibres which have been shown to be elastic fibres under the electron microscope (Tunbridge quoted by Rothman).

(2) A lowered tensile strength of the skin so that it splits with injury. The connective tissue fibres are thin with fewer cross connexions and, according to Rothman, slide more readily on each other when stretched.

Rollhauser (quoted by Rothman) states that differences of tensile strength of the skin are paralleled by the tensile strength of tendons and other fibrillary structures. This explains the associated laxity of joint capsules and tendons. The delay in healing may be due to this increased elasticity of the skin keeping the wound apart, the thin loose collagen that is reformed being of low tensile strength. The tensile strength of the skin, according to Rothman, is less in infancy than in old age, the fibres becoming thicker and more matted together with time. It may be, therefore, that the disability in Ehlers-Danlos syndrome, of splitting of the skin with trauma, will become less obvious with time. This inherited abnormality affects other mesoblastic tissues such as bone and ligaments and explains the dystrophy of the spinal bones and phalanges which this patient presents.

REFERENCE

ROTHMAN, S. (1954) Physiology and Biochemistry of the Skin. Chicago; p. 450.

The following cases were also shown:

Poikiloderma with Mycosis Fungoides.—Dr. BRIAN RUSSELL.

Follicultis Ulerythematosa Reticulata (Atrophoderma Vermicularis).—Dr. S. GOLD.

? Purpura Annularis Telangiectodes.—Dr. D. C. G. BETT (for Dr. BRIAN RUSSELL).

Parapsoriasis Variegata.—Dr. A. SCOTT (for Dr. P. BORRIE).

Dermatomyositis of One Arm.—Dr. I. MARTIN-SCOTT.

Acne Necrotica with Alopecia Universalis.—Dr. BETHEL SOLOMONS.

Arteriovenous Aneurysm of Forearm with Chronic Œdema.—Dr. A. JARRETT.

Histiocytoma.—Dr. P. J. HARE.

Darier's Disease.—Dr. LOUIS FORMAN and Dr. A. PORTER.

Benign Mucous Membrane Pemphigus.—Dr. LOUIS FORMAN.

Dr. H. HABER read a short paper entitled **Solitary Dyskeratosis.**

Section of Pædiatrics

President—D. V. HUBBLE, M.D., F.R.C.P.

[*April* 26, 1957]

Continued from November *Proceedings*, *p. 930*

The Changing Ætiology of Erythema Nodosum in Children

[*Summary*]

By JOHN LORBER, B.A., M.D., M.R.C.P., and T. COLVER, M.D.

IN a consecutive series of 106 children with erythema nodosum seen in Sheffield between January 1951 and December 1956, 66 (62%) were tuberculin positive as a result of tuberculous infection, 5 (5%) followed BCG vaccination and 35 (33%) were tuberculin negative. These figures contrast with an 88% incidence of tuberculous infection among 100 children reported by Doxiadis partly from the same unit in 1949.

There was a progressively falling proportion of children with a positive tuberculin reaction. 73% of 49 children with erythema nodosum seen in 1951/53, and only 53% of 57 seen in 1954/56, were tuberculin positive.

A positive tuberculin reaction is not necessarily an indication that tuberculosis was the only or the main predisposing factor unless there is evidence of recent tuberculin conversion, the presence of an active tuberculous lesion and other possible causes having been excluded. An active primary tuberculous lesion was seen in 46 children (43%) in the whole series. The proportion was 55% in children seen during 1951/53 and 33% in 1954/56. Even among these there were 7 with a severe preceding sore throat and 4 had beta-hæmolytic streptococci in their throat swabs. 10 of the 46 children developed various forms of tuberculous diseases (apart from the erythema nodosum and the primary complex) during observation. For this reason it is suggested that children with active primary tuberculosis associated with erythema nodosum should be given anti-tuberculous chemotherapy. In 20 children (19%) the only evidence of tuberculosis was a positive skin test. This proportion was about the expected incidence of positive reactors in the child population of the appropriate age groups during the years of this study. None developed tuberculous complications. 9 had evidence of preceding throat infection. Tuberculosis probably played an ætiological role in only a few, if any, in this group of 20.

5 children developed erythema nodosum after BCG vaccination, and in 4 this occurred at the time of tuberculin conversion. Nevertheless, other factors were present in 3 of them.

Among 35 tuberculin-negative children 17 complained of a preceding pharyngitis and in 10 laboratory evidence of a beta-hæmolytic streptococcal infection was obtained.

It is probable that multiple simultaneous factors are often responsible for the eruption of erythema nodosum.

Relapse of the erythema nodosum occurred in 6 cases and multiple cases occurred in 3 families.

[This paper will be published in full in *Arch. Dis. Childh.*]

[*June* 15, 1957]

MEETING HELD AT THE CHILDREN'S HOSPITAL, BIRMINGHAM

THE following cases and specimens were shown:

(1) **Hemiatropy of Face. (2) Nephrosis. (3) Hypogammaglobulinæmia. (4) Early Hepato-Lenticular Degeneration. (5) Pure Red Cell Anæmia. (6) Female Intersex Without Adrenal Hyperplasia. (7) Megaloblastic Anæmia with Steatorrhœa.**—Professor J. M. SMELLIE.

Male Pseudohermaphrodite.—Dr. W. H. P. CANT and Mr. V. S. BROOKES.

Lymphosarcoma.—Dr. W. H. P. CANT and Professor E. BRODIE HUGHES.

Primary Hypopituitary Dwarfism.—Dr. W. H. P. CANT.

Congenital Obliteration of Bile Ducts, Treated Surgically.—Dr. A. L. SMALLWOOD and Mr. A. GOUREVITCH.

Temporary Diabetes Mellitus.—Dr. A. L. SMALLWOOD.

Carcinoma of the Adrenal Cortex with Virilism.—Dr. A. L. SMALLWOOD and Mr. A. GOUREVITCH.

(1) Nephrosis. (2) Nephrosis (Under Treatment for Three years). **(3) Acute Nephritis in an Infant Associated with an Acute Hæmolytic Anæmia, Progressing to Chronic Nephritis and Hypertension. (4) Infantile Cortical Hyperostosis. (5) Milk Allergy** (Presenting with Ascites).—Dr. O. H. WOLFF.

Carcinoma of Ovary.—Mr. G. H. BAINES.

Congenital Obliteration of the Bile Ducts.—Dr. W. H. P. CANT and Mr. A. GOUREVITCH.

Bilateral Ectopic Ureters.—Mr. V. S. BROOKES and Dr. O. H. WOLFF.

Œsophageal Stricture Following Hiatus Hernia Treated with Colonic Graft.—Mr. A. L. D'ABREU and Dr. O. H. WOLFF.

(1) Hiatus Hernia. (2) Œsophageal Stricture Treated by Excision and Colon Transplant.—Mr. A. L. D'ABREU and Dr. O. H. WOLFF.

Extradural Abscess.—Mr. A. INNES and Mr. E. TURNER.

Fibrocystic Disease of the Pancreas.—Dr. F. BRAID.

(1) Fibrocystic Disease of the Pancreas. (2) Banti's Syndrome.—Dr. F. BRAID and Dr. C. G. PARSONS.

(1) Fibrocystic Disease of the Pancreas. (2) ? Cirrhosis of the Liver. (3) Miliary Tuberculosis, Abdominal and Intracranial Calcification.—Dr. F. BRAID.

(1) Intracranial Dermoid Tumour. (2) Klippel-Feil Deformity.—Dr. C. T. PARSONS and Mr. E. TURNER.

Hypothalamic Glioma.—Dr. H. EVERLEY JONES and Professor E. BRODIE HUGHES.

Hypothalamic Glioma.—Dr. F. BRAID.

Hypothalamic Tumour.—By permission of Dr. H. EVERLEY JONES.

Hypothalamic Tumour.—Dr. F. BRAID.

Cine-angiocardiography in Acyanotic Heart Disease of Infancy

By R. ASTLEY, M.D., D.M.R.

The Children's Hospital, Birmingham

THE various forms of congenital heart disease that are associated with a shunt of blood from the systemic to the pulmonary circulation—commonly, isolated septal defects and patency of the ductus arteriosus—are important causes of death in small children, particularly in the first year of life. Oldham (1957) analysed a series of 100 consecutive infants in whom congenital heart disease was causing disability. There were 39 with a defect causing a left-to-right shunt, including 9 with an isolated patent ductus; 19 (including 5 with a patent ductus) died within their first year.

Thus diagnosis in this group and, in particular, the localization of the site of the left-to-right shunt, is important since a patent ductus is so readily treatable surgically. However, this localization may be a difficult problem as the physical signs are often atypical in the very young; for instance, the continuous murmur of a patent ductus is often absent. Cardiac catheterization has its technical difficulties at this age and angiocardiography with simple methods at one to two pictures per second has proved disappointing. Therefore a series of small children has been investigated by cine-angiocardiography, to determine whether this method gave improved or simplified diagnosis.

The radiographic technique employed was that described previously (Astley and Oldham, 1956), using a Philips image intensifier and a 16 mm. cine camera. The camera was linked to a General Radiological Electronic generator so that each cine frame was exposed for 0·002 second as an individual high-speed radiograph, thus reducing radiation dosage and eliminating movement blurring.

Cine-angiocardiograms were obtained in 35 small children with a left-to-right shunt; there was a patent ductus in 7, an aortic-pulmonary fistula in one and atrial or ventricular septal defects in 27. These 35 formed part of a larger series of 136 cine-angiocardiograms containing all forms of congenital heart disease and part of a series of 405 angiocardiograms when examinations by full-sized films were included.

The radiographic signs that proved useful in patency of the ductus arteriosus (or aortic pulmonary fistula) were a dilution filling defect in the pulmonary artery and persistence of pulmonary artery filling (or re-filling) after the right heart chambers had emptied. These two signs were seen in all instances. With an uncomplicated septal defect, the most important feature was persistent filling or re-filling of the right atrium and/or right ventricle. A dilution filling defect in one of these chambers was often seen. In a number of children there was also a small reverse (right-to-left) shunt seen in the early stages of the angiocardiogram.

Initially, the interpretation proved less straightforward than in cyanotic heart disease. At the outset a number of false interpretations were made but with increasing experience it was found that a very definite distinction could be drawn between a patent ductus and a septal defect. The exact localization of a septal defect was less definite but often possible.

At first, when the venous angiocardiogram indicated a patent ductus, this was confirmed by counter-current cine-aortography. With increasing experience this confirmation became unnecessary and sole reliance could usually be placed on the cine-angiocardiogram, a simpler procedure that also had the advantage of indicating any associated cardiac defects.

An incidental advantage of the technique was the need for less anæsthesia. Complete cessation of movement was not necessary to obtain still pictures since each cine frame was exposed for a much shorter duration that is usually possible on full-sized films. With sedation by the Toronto modification of the "lytic cocktail" (Rowe, Vlad and Keith, 1956) the disturbance to the patient was usually slight and sometimes his general condition even appeared to be improved by the procedure.

A cine film was shown to demonstrate the cine-angiocardiographic evidence of patent ductus arteriosus, aortic-pulmonary fistula and uncomplicated septal defects.

Grateful acknowledgments are due to Dr. Clifford Parsons, who has been very closely associated with this study. The technique and evaluation of the radiographic signs will be described more fully elsewhere.

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The Association of Acute Appendicitis with Infective Diarrhœa

By K. B. Rogers, M.D.

The Children's Hospital, Birmingham

This is a preliminary report of the work of the pathology departments and the surgeons of the Birmingham Children's Hospital and it will be reported more fully later by all those concerned.

At this hospital the routine bacteriological examinations are designed to ensure that all non-lactose fermenting bacilli, from any site, are fully examined to ensure that any salmonellæ or shigellæ are identified. These methods allowed both *Shig. sonnei* and salmonellæ to be identified in the pus from the peritoneal cavities of cases of perforated appendicitis: it was also noted that some children, who had been admitted for appendicectomy, developed dysentery due to the same organisms a few days after operation.

In 1956 the proximal third of every appendix was examined bacteriologically whilst the distal portion was used for histological examinations. There were 250 appendicectomies: 170 appendices were cultured and 12 yielded *Shig. sonnei*. All of the appendices from which these strains of *Shig. sonnei* were isolated showed histological evidence of acute inflammation: *Salm. heidelberg* was isolated from one appendix which also showed histological evidence of inflammation.

Eleven of the strains of *Shig. sonnei*, and the strain of salmonella, were identified by slide agglutinations of emulsions made from colonies picked off desoxycholate citrate medium, the morning after each of these appendicectomies had been performed. The twelfth strain of *Shig. sonnei* was isolated a day later from a subculture made on to a desoxycholate citrate plate, from selenite fluid enrichment medium in which the specimen had been growing for eighteen hours. The identity of each strain was verified by tube agglutination and biochemical testing (Rogers, 1954*a*): each strain was also tested for its sensitivity to antibiotics and sulphonamides.

As soon as a strain was identified the patient was transferred to the isolation ward and was given appropriate chemotherapy. The rapid identification of all these strains, at a time when the intestines of the patient were quiet following the operative interference, allowed all the infected children to be removed to the isolation ward before any post-operative diarrhœa developed. The introduction of chemotherapy, within a day of operation, may have aborted any attacks of diarrhœa or the patients may have only been carriers, but none of these patients developed diarrhœa: chemoprophylaxis was given to all the other children in the ward to which the infectious case had been originally admitted (Rogers, 1954*b*). It is noteworthy that during the dysentery pandemic of 1956 no surgical ward had to be closed to admissions because of the spread of dysentery.

The appendices were also cultured to demonstrate the presence of other organisms, including clostridia, by the techniques previously described (Rogers and Heslop, 1948). Except for the anaerobic cultures, and the incubation of the MacConkey and desoxycholate citrate plates, all these cultures were incubated in an atmosphere of 10% carbon dioxide: this probably accounted for the finding of Lancefield group F hæmolytic streptococci in 11% of the appendices, as Liu (1954) has shown that these "minute" group F streptococci grow better in an increased concentration of carbon dioxide. A few of the appendices provided heavy growths of pneumococci and *H. influenzæ*, and 34% grew *Cl. welchii*.

It is not suggested that salmonellæ or shigellæ are the cause of acute appendicitis but that sometimes acute appendicitis is associated with an enteral infection and that if cultures are made to demonstrate the presence of these intestinal pathogens it is possible to remove an infectious case from a ward before cross-infection occurs. It must be emphasized that there was a pandemic of Sonne dysentery in the year in which the above investigation was made and this may account for the relatively large proportion of the appendices from which *Shig. sonnei* was isolated.

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The Treatment of Juvenile Thyrotoxicosis with Potassium Perchlorate

By Professor J. M. Smellie
The Children's Hospital, Birmingham

The infrequency of hyperthyroidism in children renders knowledge and experience of its treatment limited and the merits and demerits of various therapeutic procedures are controversial. 6 children, aged from 6 years to 13 years have been treated with 200–300 mg. of potassium perchlorate daily. The duration of treatment has been from nine months to three years. In all, satisfactory clinical progress has been achieved and the children are now euthyroid. The only undesirable side-effect encountered has been a minor degree of hypothyroidism in two instances; none has had any gastro-intestinal upset. Iodine must not be given during perchlorate treatment.

Experience to date would appear to indicate that treatment will be required for a period of two to three years and perhaps even up to puberty.

It is not yet possible to say whether potassium perchlorate will restore all hyperthyroid children to a euthyroid state and thus render surgery unnecessary, but it does at least delay consideration of any operative procedures without detriment to the patient.

[This paper is published in full in the *Lancet* (1957) ii, 1035.]

Duodenal Obstruction in the New-born

By A. Gourevitch, F.R.C.S.
United Birmingham Hospitals

(In presenting this paper, I wish to record that Mr. Michael Lord has participated in the work of its preparation.)

Congenital abnormalities are responsible for the hard core of neonatal deaths. Notable among these are congenital abnormalities of the bowel, and, in particular, obstruction.

The results of operative treatment particularly in the intrinsic group, have been disappointing and a number of factors, which I shall examine here, have contributed to this.

This paper concerns a series of 58 babies with duodenal obstruction admitted to the Birmingham Children's Hospital between the years 1939 and 1956. 49 were operated on: of the remainder 7 were considered too ill for surgery, a mongol was left, and in another, a malrotation, operation was not indicated.

I have separated duodenal obstruction from the rest of neonatal intestinal obstruction to compare conditions having a similar clinical and radiological picture. Furthermore, I believe that duodenal obstruction is ætiologically and in its natural history a different condition from jejuno-ileal atresia.

I have divided this series into intrinsic and extrinsic groups (Fig. 1).
3 types of intrinsic obstruction have been encountered (Fig. 2).

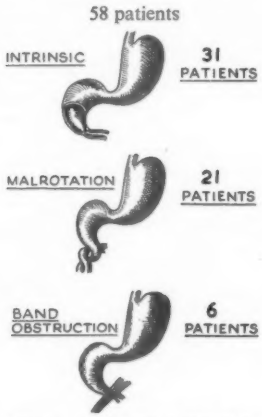


FIG. 1.—Duodenal obstruction.
Three main groups.

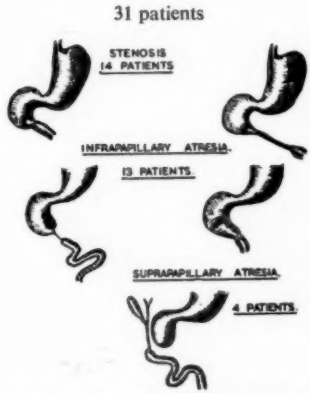


FIG. 2.—Types of intrinsic duodenal obstruction.

MULTIPLE LESIONS

These lesions can occur together in any combination (Fig. 3).
Excluding malrotation + bands, we have had 10 cases of multiple lesions in 49 operated patients.

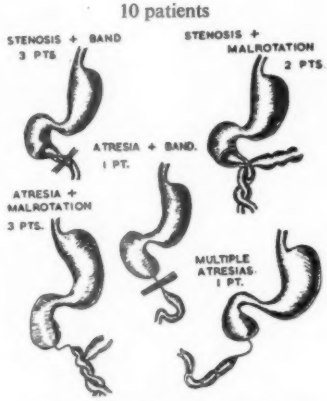


FIG. 3.—Duodenal obstruction.
Multiple lesions.

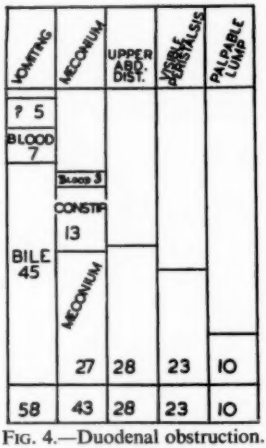


FIG. 4.—Duodenal obstruction.
Clinical findings.

The association of malrotation and bands being well known is unlikely to be missed. The chief danger lies in the co-existence of duodenal stenosis with another lesion. In 5 such patients, the intrinsic lesion was overlooked with fatal results. Clearly, it is not enough just to divide a band that crosses the duodenum, or merely to untwist a volvulus. Even if the distal bowel fills, this is no proof of the absence of stenosis. Where doubt exists, a short-circuiting operation should be done.

There were 7 mongols among these babies. 4 of these had cardiac anomalies, 1 other had congenital hydronephrosis and hydro-ureters. There were no other such gross developmental abnormalities in the series. Operation is, therefore, well worth while.

Clinical Picture (Fig. 4)

Sustained vomiting soon after birth is the sheet-anchor of diagnosis. Every child in the series vomited, the majority vomited copious amounts of bile. 13 only were constipated; the passage of meconium is therefore misleading.

Diagnosis

The value of the plain X-ray film can hardly be over-emphasized. We X-ray every child in whom obstruction is suspected. In most cases there is no need for barium which has obvious disadvantages.

Dr. R. Astley, Radiologist to the Birmingham Children's Hospital, screens the baby, who lies in the left lateral position, which favours the entry of gas into the duodenum; 2 X-ray films (Figs. 5 and 6).



Fig. 5.—Plain A.P. film of abdomen. Intrinsic duodenal obstruction.



Fig. 6.—Plain lateral film of abdomen. Intrinsic duodenal obstruction.

The features in duodenal obstruction are:

(1) Considerable dilatation of the duodenum.

(2) The presence of a small amount of gas in the distal bowel in stenoses and malrotations.

Pre-operative Preparation

It is advisable to allow a delay of several hours after X-ray. The child gets chilled as a result of the examination. It is unusual for these children to be severely dehydrated. We nearly always introduce a needle into a vein, and give fluid and electrolyte, if necessary. The stomach is emptied by Ryle's tube.

Anæsthetic

This is usually gas and oxygen in equal proportions, supplemented by scoline. The relaxant has made the operation technically much simpler. An endotracheal tube is quite essential: its introduction into a tiny larynx needs a lot of practice.

Operation

The incision should be a long one; there must be room for a careful but rapid inspection of the whole abdomen. As soon as the peritoneal cavity is opened, the whole of the mid-gut is exteriorized. This manœuvre is essential, without it one is literally working in the dark. The cæcum is identified, if it is not in the right iliac fossa, a malrotation is present. A finger and thumb are then passed round the root of the mesentery. If there is a volvulus there is a sensation as if a knot had been tied in the root of the mesentery. The volvulus, which is usually clockwise, is untwisted.

The duodenum is then inspected throughout its length, and if there is imperfect rotation of the bowel, its whole length may very well be visible; and it will be unnaturally long and convoluted. All bands are divided as stressed by Ladd of Boston many years ago. Furthermore, there may be a large colic vein compressing the duodenum and so requiring division.

The jejunum must be seen to fill. The stomach tube should be fed on into the jejunum to demonstrate its patency (not always an easy manœuvre).

If an intrinsic obstruction is present, the duodenum will be seen to be dilated and hypertrophied, it may be as large as the stomach. It may end as a blind sac. Even if this appearance is not seen, *no useful purpose is served in trying to locate a diaphragm.*

Preliminary X-rays, and the appearances at operation will have made the diagnosis certain. If a diagnosis of duodenal obstruction has been made it is never safe merely to divide bands, assuming them to be the sole cause of the obstruction. *There is almost always an intrinsic obstruction as well.* I perform a duodeno-jejunostomy, using 3–0 chromic atraumatic suture mounted on a 30 mm. hand needle, and the anastomosis is done in 2 layers. After operation 20–60 ml. of blood (depending on weight and blood loss) are injected by syringe.

Results

During the years 1952 and 1953, I noticed that babies with intrinsic obstruction were dying anything up to three weeks after operation, with continuing bile aspiration or vomiting, indicating that obstruction was unrelieved; and yet at autopsy the anastomosis was intact and patent. Clearly, the anastomosis was not functioning. I knew that others had had the same experience.

The stomach and duodenum seemed incapable of transferring fluid to the collapsed jejunum. It seemed rational, therefore, to introduce fluid directly into the jejunum via a Ryle's tube passed down the œsophagus and to force the fluid in with a syringe. I used this method for over a year, but it had several disadvantages:

(1) It meant a tube in contact with the stoma for anything up to three weeks.
(2) A second tube had to be introduced for gastric aspiration.
(3) There was no certainty that the jejunal tube would not slip back into the duodenum.

At this stage Mr. Peter Bevan suggested a feeding jejunostomy in addition to the anastomosis. Accordingly in November 1954 for the first time, I sewed a fine soft polythene tube into the jejunum in a case of duodenal atresia. The child was fed down the tube. The tube was taken out on the ninth day, after it had been demonstrated that carmine introduced orally was passed *per anum.* The child thrived and was ready to go home on the twenty-first day, when he aspirated vomit and died. I used this technique on 4 subsequent occasions with 3 recoveries and 1 death. The death was in a premature infant, and peritonitis was found at autopsy with an intact anastomosis, presumably due to soiling of the peritoneum at operation.

I have since then, in babies subsequent to this series, performed a feeding jejunostomy as a routine using a very fine soft rubber catheter, rubber being softer than polythene. Usually it is possible to do a formal Witzel procedure which obviates the danger of leakage. There is no doubt that after an interval of time, the bowel, receiving its normal stimulus, starts to work spontaneously.

The method is not foolproof, but it does introduce fluid directly into bowel which lacks the normal stimulus to contraction, and it has one other advantage, it spares veins and offers a ready avenue for the introduction of fluid, electrolyte and calories, so that everyone gets more sleep.

Post-operative Management

These babies have generally been under the combined care of a surgeon and a pædiatrician. They are the particular care of a senior resident officer who checks their intravenous schedules twice a day and cares for them most diligently. Assessment of the child's state has been almost entirely clinical, using serum analyses as an occasional check; this method has proved quite adequate. Daily serum electrolyte estimations means constantly withdrawing blood from a small baby with a diminishing supply of veins. Contrary to what I used to believe, these babies do not present a complex biochemical problem, not to be compared, for example, with that of a severe gastro-enteritis.

Mortality

There have been 49 operations and 26 deaths—a formidable operative mortality of 52%. In trying to assess the causes of death after operation in a small series such as this, spread over seventeen years, it has to be remembered that any lessening in mortality may merely reflect the increasing effectiveness of surgery and anæsthesia, rather than the virtue of any particular device or manœuvre. Looking at the series as a whole, it is clear that in a fair

proportion of these babies, operation for one reason and another has been technically ineffective.

Out of the 26 deaths:

(1) The anastomosis has leaked three times.
(2) There has been an unreduced volvulus on two occasions.
(3) A stenosis has been overlooked three times.
(4) Multiple atresias have been overlooked once.
(5) Frank general peritonitis has occurred twice, presumably due to peritoneal soiling.

It does seem, therefore, that advances can be made by scrupulous attention to every detail of the technical conduct of the operation.

I have arbitrarily divided the whole series into three groups of 19, 19 and 20 patients in chronological order, to see whether there has been any noticeable improvement over the years.

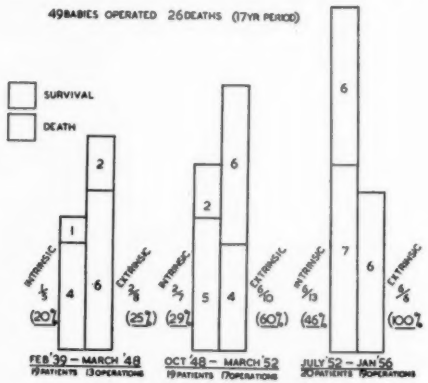


FIG. 7.—Duodenal obstruction.
Survivals.

A number of features stand out (Fig. 7):

(1) *The high death-rate and low operability rate in* series 1.—Actually the first 11 babies admitted, died, 6 with operation, 5 without. At this stage, I think it fair to say that surgeons were unfamiliar with the problem of the neonatal belly.

(2) In series 2, the death-rate has fallen, but is still high in both intrinsic and extrinsic obstruction.

(3) In series 3, there is no mortality in extrinsic obstruction, but still a high one in intrinsic obstruction due probably to technical faults, but also to the non-functioning though intact anastomosis.

Of the last 4 intrinsic obstructions, all of whom had a jejunostomy, 3 survived. Whereas three or four years ago it was an event to salvage an intrinsic obstruction, I should now be disappointed if we did not save 3 out of 4, or even 4 out of 5.

All extrinsic obstructions should be recovered.

I should like to express my thanks to my medical and surgical colleagues at the Birmingham Children's Hospital for allowing me access to case records. To the resident staff for all their help. To my registrar, Mr. M. Lord, for helping me to collect clinical information. To the nursing staff of the Birmingham Children's Hospital, for caring for these babies. To Dr. R. Astley, radiologist at the Birmingham Children's Hospital. To Dr. H. S. Baar, lately pathologist at the Birmingham Children's Hospital.

Section of Proctology

President—RONALD W. RAVEN, O.B.E., T.D., F.R.C.S.

[*June* 19, 1957]

DISCUSSION ON MAJOR SURGERY IN CARCINOMA OF THE RECTUM WITH OR WITHOUT COLOSTOMY, EXCLUDING THE ANAL CANAL AND INCLUDING THE RECTOSIGMOID

Dr. Cuthbert E. Dukes:

General Results of Surgical Treatment

Our discussion is concerned chiefly with comparisons of alternative methods in the surgical treatment of rectal cancer, and my function as opener is to present a picture of the general overall results.

The St. Mark's Hospital statistics for the twenty-five years 1928–52 inclusive may be summarized as follows:

A total of 3,596 rectal cancer patients were admitted to hospital or seen in the Outpatient Department.

2,447 of these were treated by a surgical operation which removed the primary tumour.

The overall operation mortality of these surgically treated cases was 9·4%.

Every possible endeavour was made to keep in touch with operation survivors and only 28 have not been traced. These are assumed to be dead. Since they constitute only 1·1% of all cases they exert no appreciable effect on the statistics.

The crude five-year survival rate of all patients treated by surgical removal of the primary tumour (after excluding operation deaths) was 48·3%.

When allowance was made for deaths due to intercurrent diseases the corrected five-year survival rate was found to be 57·4% (Table I).

TABLE I.—SURGICAL TREATMENT OF RECTAL CANCER AT ST. MARK'S HOSPITAL 1928–1952

Total cases of C.R. admitted to St. Mark's or seen in out-patients' department	3,596
Number treated by surgical removal of primary tumour ..	2,447
Overall operative mortality ..	9·4%
Crude five-year survival rate of patients in whom primary tumour was removed (operation deaths excluded)	48·3%
Corrected five-year survival rate	57·4%

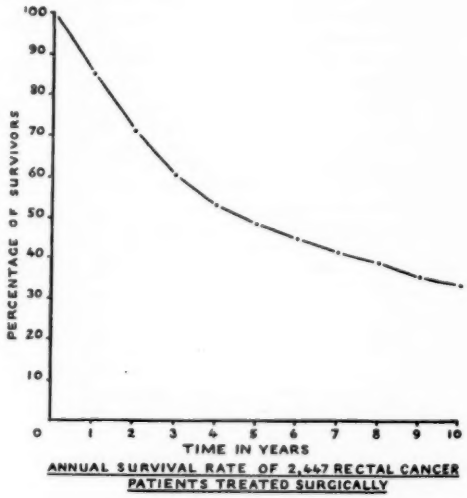


FIG. 1.

All survival rates have been calculated by actuarial methods and the crude survival rate curve for a period of ten years is shown in Fig. 1.

During the period I have reviewed (1928–1952) several different operations have been employed in the surgical treatment of rectal cancer, and subsequent speakers will point

out their advantages and disadvantages. During the last few months with the help of my research assistant, Mr. H. J. R. Bussey, I have been analysing the results of every form of surgical treatment at St. Mark's and have been impressed by the importance of ensuring that any groups compared should be of similar constitution with respect to age and sex and that the operations compared should date from approximately the same period of time.

Influence of Age of Patient on Survival Rates

The crude five-year survival rate merely states the percentage of individuals still living after five years. Some of those who failed to live for five years died of cancer and some from other causes, but the crude five-year survival rate makes no distinction between deaths due to cancer and deaths due to intercurrent diseases. Obviously therefore the crude five-year survival rate must be much affected by the average age of patients at the time of treatment: for example, the percentage of five-year survivors is likely to be considerably less from a group of patients with an average age of 70 than for another group with an average age of 60. This point is of special importance in relation to rectal cancer because the risk of dying from other causes increases rapidly just at the time of life when many patients receive surgical treatment.

It might be possible in a small series of patients to ascertain the cause of death in each one and then exclude from calculation all deaths not due to cancer within the five-year period, but in a big series this direct method is impracticable and it is easier and probably more accurate to proceed indirectly and make allowance for intercurrent deaths by making use of data provided by life tables. When a correction is made for the estimated probability of dying from causes other than cancer the term "corrected survival rate" is used.

There is more than one statistical device for producing a corrected survival rate, and I consulted Dr. Percy Stocks as to the best to adopt for our records at St. Mark's, and he recommended that described by Paterson, Tod and Russell in their book "The Results of Radium and X-ray Therapy in Malignant Disease" (Christie Hospital, 1950).

The principle is that one calculates from the standard death-rate appropriate to each age group the probability of survival in each age group for a further period of five years. This gives a factor known as Po. The crude survival rate experienced is then divided by this factor, and this corrects for deaths due to intercurrent diseases in the specified period. Dr. Stocks (1957) very kindly supplied additional statistical tables to cover the years 1931 and 1950 and my research assistant, Mr. Bussey, has calculated the correction factor separately for each of the five-year periods included in this review (1928–1952), because standard death-rates have not remained stationary throughout the twenty-five years.

The corrected survival rate gives a much more accurate picture of what is actually accomplished by surgical treatment than does the crude survival rate, and is therefore of special value when comparisons are being made between different surgical operations, especially if there is any difference in age and sex distribution of patients.

So far we have been considering the age of a group of rectal cancer patients only because of its obvious effect on the risk of dying from intercurrent diseases, but age is of importance also because the rate of growth of a rectal cancer tends to slow down with advancing years. There has long been a general clinical impression that this is so, though it has been difficult to prove by statistical evidence (Lees and Park, 1949).

The simplest way of demonstrating the effect of advancing years on rate of growth is to group rectal cancer patients according to age and then compare the percentage of cases with metastases in each age group. This information is set out in Table II, from which it

Table II.—Relation of Age of Patient to Incidence of Lymphatic Metastases

	Males			Females		
Age group	No. of patients	No. with metastases	Percentage with metastases	No. of patients	No. with metastases	Percentage with metastases
Under 40	84	61	72·6	67	50	74·6
40–49	176	93	52·8	112	75	67·0
50–59	414	209	50·5	218	114	52·3
60–69	544	245	45·0	243	132	54·3
70 and over	270	109	40·4	128	62	48·4
Total	1,488	717	48·2	768	433	56·4

will be seen that in patients under 40 years of age the incidence of lymphatic metastases was over 70%, and that it decreased steadily in middle age.

Another way of demonstrating that the growth potential of rectal cancer slows down

with advancing years is by comparison of the average age of patients at successive stages in the development of malignancy. This brings to light the somewhat paradoxical fact that the average age of early stage patients is older than the average age of later stage patients, which seems at first to be contrary to expectations, because we might have anticipated that the average age of A cases would be younger than B, and the B cases would be younger than the C. The exact opposite was found to be the case. The actual figures for this series were as follows: For males the average age for A cases was 61·97, for B cases 61·23, and for C cases 58·50 years. The corresponding figures for females were A cases 60·10, B cases 59·54, and C cases 56·62 years (Table III). This point is worth mentioning because

TABLE III.—CANCER OF RECTUM
Average Age in Years of A, B *and* C *Cases at Time of Surgical Treatment*

Cases	Men	Women
A	61·97	60·10
B	61·23	59·54
C	58·50	56·62

it is often assumed that if comparisons are made of survival rates of tumours which have been classified according to stages of development then the average age of the patients need not be considered, but this would only be justified if the average age at each stage was the same. In rectal cancer this is not so. Stage I or A cases are on the average about three and a half years older than the Stage III or C cases.

We gain a truer picture of what is actually accomplished by surgery if we take the age of patients into consideration when comparing survival rates of A, B and C cases and apply a correction factor to make allowance for deaths from intercurrent diseases. The effect of this is greatly to improve the survival rate of A cases, because this being the oldest group is the one in which the greatest number of intercurrent deaths might be expected. The application of the correction factor has less effect on the crude survival rate of B cases and still less on C cases (Table IV).

TABLE IV.—CANCER OF RECTUM
Five-year Survival for A, B *and* C *Cases*
(Operation deaths excluded)

MEN				WOMEN			
No. of cases	Stage	Crude five-year survival rate %	Corrected five-year survival rate %	No. of cases	Stage	Crude five-year survival rate %	Corrected five-year survival rate %
206	A	80·4	99·9	129	A	81·8	93·8
565	B	61·3	76·0	206	B	71·6	82·0
717	C	26·1	31·3	433	C	29·1	32·7

INFLUENCE OF SEX ON SURVIVAL RATES

When considering the effect of sex on survival after rectal cancer we should first recall that the natural expectation of life after middle age is not so good for men as for women. The extent of this sex difference varies with locality, but here in London now the death-rate for men between the ages of 45 and 64 is actually twice as high as for women in this same age group (Scott, 1955). Moreover at the age of 65 (when so many cases of rectal cancer receive surgical treatment) the natural expectation of life for men is twelve years but fifteen for women.

The fact that rectal cancer is commoner in men than in women points to the probability of some innate constitutional sex difference. This certainly exists and I will mention some ways in which it may affect survival rates after surgical treatment.

In the first place women patients on the average are two to three years younger than men at the time of diagnosis. Secondly, at the time of surgical treatment the disease tends to be at an earlier stage of development in women than in men, as proved by the fact that A cases are relatively more numerous. Thirdly, rectal cancer tends to metastasize earlier and more frequently in women than in men.

Fourthly, in all types of major surgery for rectal cancer the operative mortality has tended to be lower for women than for men. Finally, the sex ratio in combined excisions at St. Mark's has been 33% women to 67% men, but in restorative resections the proportions have been 43% women and 57% men.

Since there are so many ways in which sex may influence survival after rectal cancer it is always desirable to calculate survival rates separately for men and women, when comparisons are being made between different operations.

Effect on Survival Rate of Decline in Operative Mortality and Rise in Resectability Rate

During the twenty-five years under review there have been many improvements in anæsthetics and in the pre- and post-operative treatment of patients, and these have resulted in a considerable decline in operative mortality and an astonishing rise in the resectability rate. The average operative mortality for this whole series was 9·4%, but it was as high as 12·8% in 1928–32 and it declined progressively to 6·8% in the period 1948–52 (Table V).

The average resectability rate for the whole period was 72·5%. It was only 46·5% in the first five-year period but it rose steadily to reach 92·7% in the last (Table VI).

Table V

St. Mark's Hospital, 1928–1952

Operative Mortality of Rectal Cancer

Period	Operations	Deaths	% Operative mortality rate
1928–32	484	62	12·8
1933–37	601	66	11·0
1938–42	595	66	11·1
1943–47	775	61	7·9
1948–52	918	62	6·8
1928–52	3,373	317	9·4

Table VI

Resectability Rate of Rectal Cancer

Total No. of cases assessed for operation	No. of cases in which growth was removed	% Resectability rate
484	225	46·5
601	346	57·6
595	413	69·4
775	612	79·0
918	851	92·7
3,373	2,447	72·5

The combined effect of these notable advances has been to enlarge the scope of surgery and to increase the total number of patients cured thereby, but it is important to notice that these improvements in the total overall results of surgery are not reflected in post-operative survival rates, because these are based on operation survivors only and not on the total cases seen or diagnosed. In fact, survival rates after surgical treatment tend to be adversely affected by both a decline in operative mortality and by a rise in the resectability rate for reasons which I will endeavour to explain.

A decline in operative mortality from 12·8% to 6·8%, such as occurred between the beginning and the end of this series, means that out of every 100 patients 6 more survived the ordeal of surgery and joined the ranks of post-operative survivors. But these 6 recruits are unlikely to be as physically fit as the rest of the group they have joined, as suggested by the fact that they would have succumbed had they undergone the ordeal of their operation when it was more severe and only survive now because it has been made easier. Their inclusion in the group of post-operation survivors tends to lower the average level of fitness and to lessen the percentage who will reach the five-year goal.

A rise in resectability rate has a similar effect. Patients who formerly were considered unfit for surgery are now placed on the operation list. Such patients must have a poorer expectation of life and in some cases an increased liability to recurrence. A lowering of the average level of health in the group of operation survivors will tend to add to the number who fall by the wayside and to lower the percentage of those who live to celebrate the fifth anniversary of their operation.

This process of dilution with relatively unfavourable material has continued progressively throughout the whole period covered by this review, yet in spite of this the five-year survival rate has not declined (Table VII). This means that surgeons to-day are as successful in

Table VII.—Five-year Post-operative Survival Rates after Surgical Treatment of Rectal Cancer at St. Mark's Hospital, 1928–1952

All Operable Cases (3,373)

Period	Crude five-year survival rate %	Corrected five-year survival rate %
1928–32	49·3	56·5
1933–37	46·2	54·5
1938–42	46·8	54·9
1943–47	53·7	63·9
1948–52	46·2	56·1
1928–52	48·3	57·4

dealing with relatively poor material as their predecessors were in selected cases twenty-five years ago.

The stationary character of the five-year survival rate naturally raises the question as to whether or not surgery has reached the limit of human achievement. There must be a limit somewhere, at any rate with existing resources. Of course the five-year survival rate is a far from delicate indicator of progress, and we know that many refinements and improvements are constantly being introduced which it fails to register. Its chief merit is that it is a convenient and easily understood way of assessing the results of surgery.

I will conclude by recalling an experience I had recently in New York, where I had been invited to participate in a panel discussion on the pathology and treatment of rectal cancer. Questions were sent up by the audience, and one concerned the relative merits of the four operations we are discussing. This provoked a lively discussion amongst the surgical members of the panel and finally the Question Master turned to me saying, "Now tell us, Dr. Dukes, which of these operations would *you* choose if you needed one yourself or for a close relative or friend?" This was the last question of the day and time was getting short, so I replied briefly as follows. "I should not choose the *operation*, but I should choose the *surgeon* who was to do it, and I should choose him with *very great care*. Then I should say to him, 'Do the operation just when and where you think best, but please promise to go to bed early the night before and to get up in good time and have a good breakfast!' It would be a relief also to be assured that the operation would not be filmed or televised!"

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Mr. A. Lawrence Abel:

The Abdomino-perineal Operation for Cancer of the Rectum

This is the fiftieth anniversary of the introduction by W. Ernest Miles of the abdomino-perineal operation for cancer of the rectum. As an old Registrar, assistant and colleague of Ernest Miles I am highly honoured to be invited to speak on this important subject in this Jubilee year.

History.—I would remind you that in 1826 Lisfranc, and later Verneuil (1873), carried out small perineal excisions for this disease with a mortality of 80% and a recurrence rate of 100%. In 1875 Kocher introduced the use of antiseptics and closed the anus before performing a perineal excision, and reduced the mortality to about 20%, though the recurrence rate remained high at 84%. In 1885 Kraske excised part of the sacrum to attain easier access and the mortality of his operation varied in different hands from 20% to 11%, but still had a recurrence rate of between 70% and 80%. So for nearly a hundred years although many surgeons attempted to cure this disease (with poor anæsthesia and no antibiotics) the mortality remained around 80% and there was over 80% recurrence.

The Miles abdomino-perineal operation.—In 1907 Ernest Miles, as a result of his researches into the lymphatic spread of the disease, introduced the attack starting high up in the abdominal cavity so as to include the maximum upward, lateral and downward spread. Ever since I became associated with him some thirty-four years ago I have used the abdomino-perineal operation for the majority of cases. During recent years the resection rate has been 94%. Less radical treatment is given only in 6% of patients with cancer of the rectum.

For example:

(1) Occasionally cases are sent to the Royal Marsden Hospital and Institute of Cancer Research, Royal Cancer Hospital, who have such extensive abdominal complications that they have obviously only a few days to live and in whom no surgical treatment is called for.

(2) In the very old and feeble, surgical diathermy is occasionally utilized to keep the rectal lumen patent. The performance of a colostomy as the only remedy is hardly ever undertaken.

(3) If at laparotomy the liver is found to be heavily affected with metastases I sometimes carry out an extended Hartmann's operation, resecting the pelvic colon and rectum to anal canal without incising the perineum.

(4) The remainder of the 6% of advanced cases have an anterior conservative resection with restoration of intestinal continuity. I would emphasize that I do not perform this

operation in any case of cancer of the rectum which appears curable, because out of 11 cases which one of my colleagues and I operated on some years ago, 7 recurred within eighteen months.

The remaining 94% of cases are treated by the radical abdomino-perineal operation. This is always preceded by a biopsy of the lesion and a few days of bowel preparation by washouts and intestinal antibiotics.

The anæsthetic.—The patient is put to sleep in bed by an injection of Omnopon 1/3 grain and scopolamine 1/150 grain. One hour later the anæsthetist gives Pentothal, and the patient is brought to the theatre unconscious. Then an intrathecal injection of 1 : 1,500 Nupercaine is given and general anæsthesia continued with nitrous oxide and oxygen only. These techniques made a great difference to the mortality. For over thirty years we have avoided ether and chloroform.

The bladder.—It is very important to empty the bladder and to keep up steady suprapubic pressure until the catheter is withdrawn, otherwise the bladder fills with air which, in pelvic operations, is worse than a bladder full of urine.

The operation.—This was demonstrated by a colour film with a commentary as follows:

A long right paramedian incision is made extending from 2·5 cm. above the umbilicus to the pubis. The fat of the abdominal wall is protected by attaching cloths to the anterior rectus sheath on both sides.

When the abdomen is open the liver is always felt to see if metastases are present. It used to be said that cases which at the time of laparotomy were found to have obvious hepatic metastases should be treated by colostomy alone. However, in 1931 I had the privilege of meeting Dr. Daniel Fiske Jones of Boston. He told me of the great benefit and prolongation of life that these patients received if a full abdomino-perineal excision was carried out. Since then the majority of my cases with hepatic metastases have been treated by the radical operation. They are of course incurable, but they die at a later date than if the primary lesion is left in situ. The majority live free of pelvic complications and have a painless death. I have seen many live over five years, one for eight and a half, and one over twelve years.

The exploration made, a wide self-retaining retractor is inserted, the intestines are packed into the upper abdomen and the table is tipped into a high Trendelenburg tilt.

Mobilizing the pelvic colon.—The pelvic colon is drawn to the right revealing the bloodless white line where the hindgut rotated and joined the parietal peritoneum—the zygotic plane. The first step is to divide the adhesions which always exist between the left side of the pelvic mesocolon and the left iliac parietal peritoneum. The peritoneal incision is carried downwards obliquely towards the recto-vesical pouch, still in the zygotic plane. Blunt dissection with a small gauze swab on a long forceps (the use of which I learned from Dr. Frank Lahey in Boston in 1931) is very satisfactory for performing a bloodless dissection of the tissues whereby the ureter is immediately seen with the spermatic (or ovarian) vessels to the outer side. Behind the ureter, the bifurcation of the common iliac artery and its two branches are quickly defined.

The internal iliac arteries.—The anterior division of the internal iliac artery is separated from the big internal iliac vein behind it by a little blunt dissection (the posterior division has, of course, come off at the bifurcation of the common iliac and gone backwards through the great sacro-sciatic notch). The next step is to pass a ligature around the anterior division of the internal iliac artery and ligate it in continuity.

Now an incision is made in the right leaf of the pelvic mesocolon with the pelvic colon drawn to the left. The bifurcation of the aorta, the right common iliac artery and its bifurcation are defined. The right ureter is seen a little to the right of the bifurcation. Blunt dissection again separates the anterior division of the internal iliac artery from the underlying vein. A catgut or thread ligature is passed round it, and it is ligated in continuity. In an average case I do not think this is an essential step, but it certainly prevents bleeding from the middle hæmorrhoidal arteries. However, if the uterus or bladder has to be removed at the same time it is a most valuable step. Miles used it invariably for a Wertheim's hysterectomy. I have done it for many years, both for a standard abdomino-perineal excision and when an abdomino-perineal and a Wertheim have to be carried out together.

The inferior mesenteric artery.—The next key point in the operation is ligature of the root of the pelvic mesocolon with its contained inferior mesenteric artery, vein and lymphatics. With the assistant pulling the pelvic colon well down, a stout ligature is passed by means of a Reverdin needle around the root of the pelvic mesocolon just above the level of the bifurcation of the abdominal aorta and firmly tied. This is at the "site of election", or "pointe critique" and is called the "Rubicon ligature" because once it is tied

there is no turning back, for the blood supply to the lower sigmoid and rectum is now cut off. A second ligature is passed and tied 2·5 cm. below the first ligature to prevent back-flow.

Before these two ligatures are tied, care is taken not to manipulate the rectum with its contained growth because there is evidence that cancer cells may be forced into the blood stream. This is one reason why I do not have another surgeon working in the perineum.

The pelvic peritoneum.—The peritoneum is now divided farther down on each side of the rectum till the incisions meet in the recto-vesical or recto-vaginal pouch. This completes the division of the peritoneum around the pelvis and the rectum is thus entirely free of peritoneal attachments.

Following this the fingers are passed into the hollow of the sacrum to strip the rectum and all the retro-rectal fat and lymphatic glands contained in the fascia propria of the rectum from the front of the sacrum down to the coccyx. The clean shining periosteum of the sacrum is the indication that the stripping is in the correct plane.

The lateral rectal ligaments.—Now the lateral ligaments of the rectum become apparent and they are divided with 14-inch scissors. Care is taken not to damage the big vessels lying to the outer side on the lateral pelvic wall. This incision is carried downwards to the fascia of the obturator internus and upper surface of the levatores ani muscles. Thus the rectum is freed on both sides down to the levatores ani. The rectum is now mobilized anteriorly with blunt or sharp dissection keeping between the fascia of the rectum and the fascia enclosing the seminal vesicles (or vagina). Thus the rectum is now free right down to the prostate in front, to the levatores ani laterally and to the coccyx posteriorly.

Division of the colon and mesocolon.—The pelvic mesocolon is now divided at right angles to the main or "Rubicon" ligature. For the first time since the abdomen was opened, one or two vessels will be seen to bleed showing that there is a good collateral circulation to the part of the bowel which is to form a terminal colostomy or artificial anus. These vessels are ligated. The incision is at right angles to the bowel so that as much as possible of the dangerous pelvic mesocolon and the greatest possible length of pelvic colon with its paracolic glands are removed.

Division of the bowel.—I use the Zachary Cope modification of the Martell three-bladed clamp—a most valuable instrument; it sterilizes the bowel by crushing it; the middle of the three blades is removed; the bowel is divided between the two remaining blades with the cautery or diathermy. Cultures taken from upwards of two hundred of these incised surfaces have remained sterile. Nevertheless, to be quite safe a plastic cap is applied over each end of the Cope–Martell clamp or a cover may be made from rubber sheeting.

The whole mass of pelvic colon, mesocolon and rectum is tucked downwards into the hollow of the sacrum. At this stage another useful step is to pass a ligature around the median sacral artery where it may be seen or felt lying on the sacral promontory. This often prevents difficult bleeding in those cases in which the coccyx has to be excised in the perineal part of the operation.

The new pelvic floor.—This is made by stripping up the peritoneum from the dorsum and base of the bladder and from the side walls of the pelvis. By gently separating and teasing with blunt dissection a nice thick, firm sheet of peritoneum with which to close the lower abdominal cavity is obtained. This is known as the "strip-tease" part of the operation. On each side wall the vas deferens is seen and the suspensory ligament of each is dissected free. In elderly subjects each vas is divided for the same reasons as when performing prostatectomy.

This newly-formed peritoneal flap is sutured by a continuous interlocking catgut stitch, first by bringing its centre or apex to the peritoneum in the region of the Rubicon ligature and then extending to the wall of the pelvis on both sides. The rough edge of the peritoneum should be carefully extroverted towards the pelvis so that on the abdominal side the peritoneum is smooth. Care is necessary on the left, where the suturing goes round the root of the bowel which is going to form the artificial anus in order to avoid including blood vessels in the stitch. When this suture is finished the pelvic cavity is completely separated by the new peritoneal flap from the abdominal cavity.

The artificial anus.—The self-retaining retractor and packs are removed. The bowel end must be brought through the anterior abdominal wall. This is effected thus: at a point one-third of the distance between the left anterior superior iliac spine and the umbilicus a circle of skin 2·5 cm. in diameter is excised. A stab wound is made through all layers of the wall and stretched. Through this the termination of the colon with its attached clamp and cap is drawn and should be found to project about 2·5 cm.

Inside the abdomen one further suture is needed. This is to close the gap between the

last 8–10 cm. of the pelvic colon and the wall of the abdomen and left iliac fossa, otherwise a knuckle of bowel may pass into it and strangulate. It is interesting that if a knuckle of small intestine does pass through such a gap it usually goes from below upwards and not from above downwards. In a case which has not had this lateral paracolic gutter closed and which develops acute obstruction a surgeon should know that three times out of four, the small intestine has passed from below upwards.

Closure of the abdomen.—The abdomen is closed: the peritoneum with catgut; the rest of the abdominal wall with stainless steel wire. The latter was brought to my attention by Dr. Thomas E. Jones of Cleveland, Ohio, twenty years ago, and I have used nothing else since for closing major abdominal wounds. If the patient is thin interrupted stitches are used; if fat, continuous. In either case the far-and-near stitch which Alan Hunt and I described nine years ago is used; the far stitch takes a bite of the linea alba and about 2·5 cm. of rectus muscle; then the near stitch the two adjacent edges of the anterior rectus sheath, making a figure of 8. It has been shown that in general abdominal work using other suture materials a little over 1% of wounds disrupt; of these 43% die. The proper use of stainless steel therefore saves nearly one-half of 1% of cases. As it is preferable not to have stitches through skin, Michel clips are used to appose the skin edges.

Fashioning the artificial anus.—The final stage in the abdominal portion of the operation is the important treatment of the last few centimetres of the colon in order to prevent peri-colostomic herniation. In my young days, a large proportion of these cases developed peri-colostomic hernias, sometimes big, sometimes small. Miles used to place one stitch above and one below between the skin and the bowel: herniations were common. For many years now a catgut suture has been inserted—first between the wall of the bowel and the peritoneum of the abdominal wall—second, another continuous interlocking layer between the anterior aponeurosis and the wall of the bowel, and finally just before the patient leaves the table, 8 or 12 stitches are placed accurately apposing the mucosa and the skin: to-day, herniations are rare. Years ago, stenosis and contraction of the opening were frequent; with this care the artificial anus retains its wide opening. I prefer to call it "artificial anus" and not "colostomy". Many people have had a grandfather or someone who had a colostomy in the old days, when a loop of bowel was brought out and when the primary disease was not removed. If the word "colostomy" is used for to-day's operation, which is curative in a large proportion of cases, the relations are apt to imagine that the patient is going to be worse with this "colostomy" than before. So to call it "artificial anus" is good psychology.

The perineal portion of the operation.—This is carried out in the right lateral position. The skin is carefully cleansed, not only because of pyogenic organisms but also because of the possibility of cancer cells having oozed out. A lotion of mercury, which Miles taught for many years will destroy cancer cells, is used. The anus is closed with a purse-string suture and the area again treated with 1 : 500 perchloride of mercury.

The incision.—A figure-of-6 incision—Miles' original incision—starts to one side of the sacro-coccygeal joint and includes a wide area of peri-anal skin and deepens vertically upwards to divide the ischiorectal fat close to the ischia and inner borders of gluteus maximus muscles. The knife is insinuated, in the male usually between the coccyx and sacrum, but in the female often below the coccyx. A deeper sweep cuts the levatores ani close to the wall of the pelvis starting on either side of the sacro-coccygeal junction. The displaced colon is now drawn out through the wound from the sacral hollow and, owing to the extent of the dissection which has been carried out from the abdominal aspect, all that remains is to dissect the lower third of the rectum and anal canal from the prostate and base of the triangular ligament avoiding damage to the bulb of the urethra which should not have an indwelling catheter. All bleeding points are carefully secured.

The toilet and closure.—The pelvic cavity remaining is relatively septic because of the disruption of innumerable lymphatics potentially bearing organisms and cancer cells. Because of this it is swabbed with 1 : 500 perchloride of mercury and then this is washed away with normal saline. The wound is covered with a layer of oil-silk into which is packed about 1–2 yards of gauze impregnated with sulphonamide. The end of the pack is left protruding and the remainder of the wound closed by some deep and some more superficial interrupted catgut sutures to draw the subcutaneous tissues together. The most comfortable stitch for the skin is subcuticular. Two or three of these are required, each 5–7·5 cm. long, and the patient can sit up the next day because the wound is comfortable. Blood transfusion is given at or towards the end of the operation.

[End of film commentary.]

The scope of the standard combined abdomino-perineal operation is shown in Fig. 1. It can easily be extended if the disease is more widespread (Figs. 2–6).

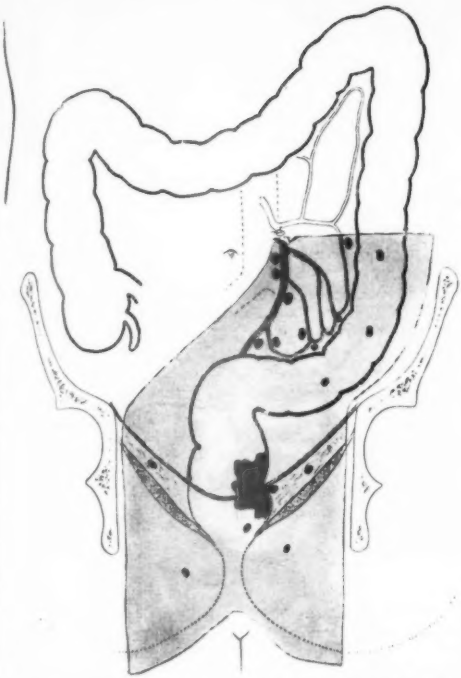


FIG. 1.—The standard combined abdomino-perineal operation.

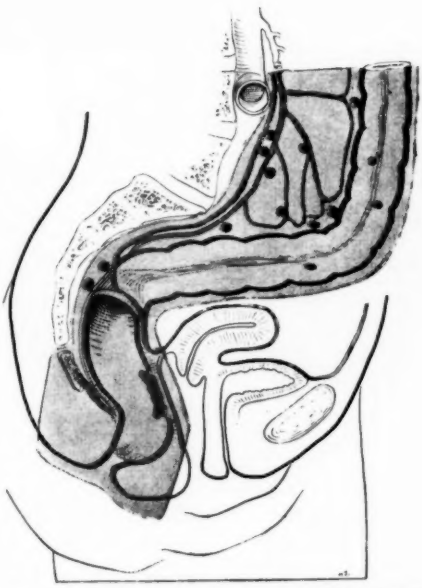
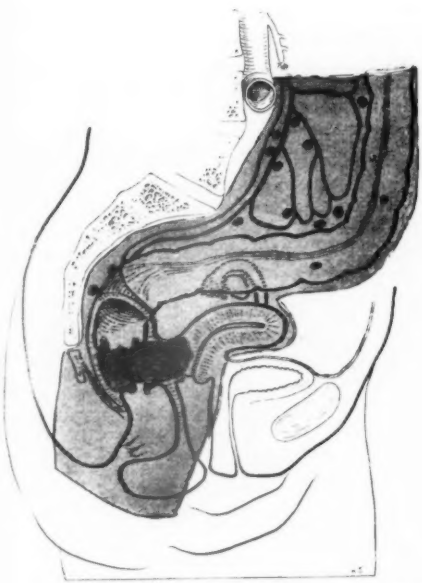


FIG. 2.—The abdomino-perineal operation extended to include the posterior wall of the vagina.



IG. 3.—The abdomino-perineal operation plus Wertheim's hysterectomy.

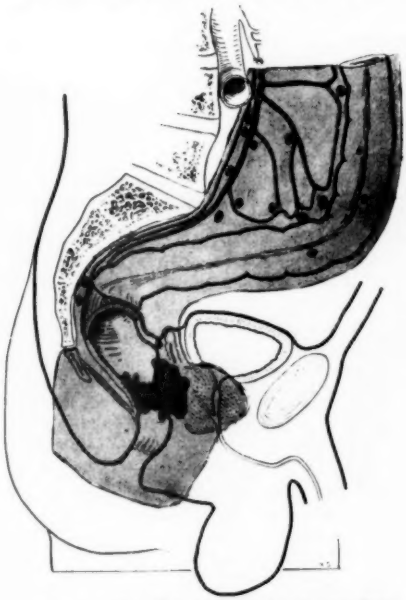


FIG. 4.—The abdomino-perineal operation plus removal of the affected prostate.

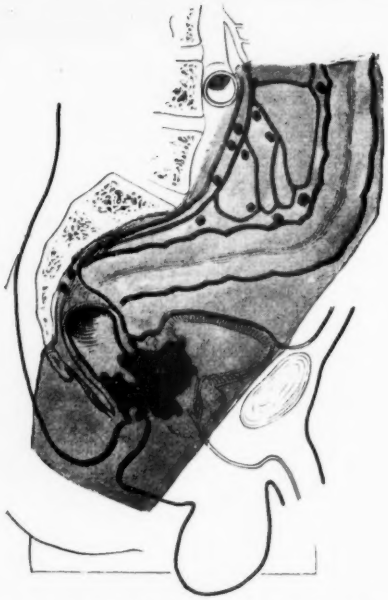


FIG. 5.—The abdomino-perineal operation plus total cystoprostatectomy.

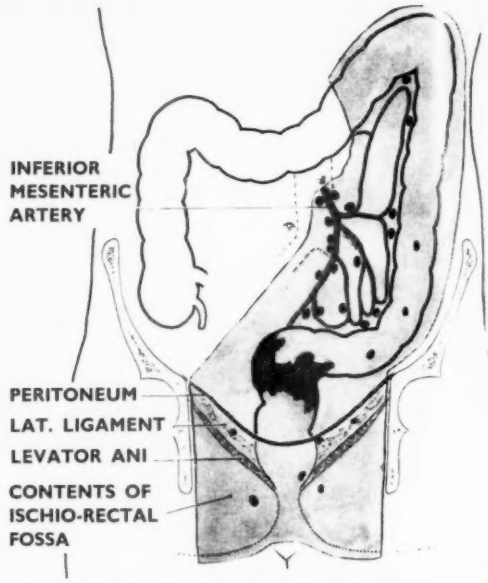


Fig. 6 shows the scope of operation for an advanced lesion at the pelvi-rectal junction. The ideal area of resection is from the left half of the transverse colon down to and including the whole rectum including ligature of the inferior mesenteric artery at its origin from the aorta. However, some patients are unable to withstand such an extensive resection as compared with the standard abdomino-perineal excision. The advantage gained, however, is the removal of the lymph nodes lying on the first 3–4 cm. of the inferior mesenteric artery. Therefore for these advanced cases the extensive operation is carried out whenever possible but the standard operation is used for a poorer risk case.

Before the days of antibiotics and modern anæsthesia the operative mortality was due to infection, pulmonary complications, peritonitis, paralytic ileus and urinary infection. Shock in those days was a big factor. To-day the majority, if not all of these, have been eliminated, and the mortality is almost limited to diseases which are as yet difficult to avoid, such as coronary catastrophe, pulmonary embolism, and only rarely infection.

With regard to results, the statistician at the Royal Marsden Hospital and Institute of Cancer Research, Royal Cancer Hospital, Mr. P. M. Paine, and my senior Registrars, Mr. Cyril Cooling and Mr. Allan Clain, have analysed 200 consecutive cases seen during 1947–1951. Of these cases 94% had the radical operation. The mortality was 5·3%. Of the survivors the five-year crude survival rates are shown by stages in Table I.

TABLE I.—CANCER OF THE RECTUM

Abdomino-perineal Excision

5-year crude survival rates by stages

(Overall resectability 94%)

Stage A	87%
Stage B	60%
Stage C	43%
All Stages	53%

Lastly, it is heartening to recall that, out of more than 1,300 operated cases, very many who appeared to be in an advanced stage of the disease and whose pathological report indicated a grave prognosis, after an abdomino-perineal excision, still attend for follow-up inspections twenty, twenty-five and even thirty years later.

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Mr. W. B. Gabriel:

Perineo-abdominal Excision

My first one-stage perineo-abdominal excision of the rectum for malignant disease (that is, without a preliminary colostomy) was done in April 1932, so that in reporting my experience for this operation to the end of 1956 I am covering a period of close on twenty-five years. The total number is 1,223. These operations were all for established malignant tumours proved by section, and perineo-abdominal excisions done for benign lesions such as polyposis or large villous tumours have been excluded from this total.

In addition there is a relatively small number of cases in which a perineo-abdominal excision was done as a second-stage procedure after a colostomy had been established. Most of these were in my early days, some before 1932. I regard these cases (39 in all) as separate from the main group. There have been only 9 in the last ten years and they have not been included in the gross figure of 1,223 given above.

GUIDING PRINCIPLES IN THE CHOICE OF TREATMENT

I favour a straight radical excision of the rectum and pelvic colon when a malignant growth develops at any level of the rectum or rectosigmoid, for the following reasons:

(1) It is generally reckoned that about 80% of intestinal cancers develop in the rectum, rectosigmoid or pelvic colon, and if one malignant growth forms in the rectum or rectosigmoid it would seem to be a mistake to conserve any part of this dangerous area.

(2) Related benign tumours are found in at least 30% of specimens removed by radical excision; some are below but more usually they are found above the main tumour and a radical excision of the rectum and pelvic colon up to a left iliac colostomy enables the risk of later malignant growths in this segment to be excluded. In a number of my cases after radical excision a pedunculated adenoma has presented at the colostomy and has easily been removed after ligation of the pedicle.

(3) Multiple malignant tumours have been found in approximately 50 cases in my series (4%). Usually the upper growth has not been diagnosed either before or during operation and only the subsequent pathological examination has shown the need for and the wisdom of a combined radical operation.

(4) The complete removal of the upward zone of spread must pay dividends in the long run and I defy any surgeon to assess accurately the extent of lymphatic spread at the time of operation. Some turn out to be better than expected, some worse, and discontinuous upward lymphatic spread is common.

(5) My opposition to restorative operations for rectosigmoid cancers is that these operations must be more lengthy and more dangerous especially in old subjects with arteriosclerosis, diverticulitis, or a short pelvic colon, and may place a greater strain on their healing capacity than a straight radical excision. Also in these days of shortage of hospital beds and expense of private wards the question of hospital morbidity is an important one. I get most of my patients with perineo-abdominal excisions out of hospital on or about the twenty-third post-operative day and some go earlier than this if it fits in with arrangements for convalescence.

(6) The great majority of patients after a radical operation have a trouble-free life and assure me that they are not worried or troubled by their colostomy. Once the perineal wound is healed only a six-monthly visit is advisable and I like these patients to appreciate that there is no need for close hospital supervision and that they can resume their normal activities. Reconstruction of a colostomy for stenosis is perhaps the most common subsequent minor procedure, and a repair operation for a sacral or perineal bulge is needed rarely. One common problem is to persuade these patients not to put on too much weight.

Selection of Cases and Preliminary Investigations

The chance of cure or relief must be given to the largest possible number of cases and, as we grow in experience and the confidence that is engendered by team work, operation is extended to late cases, bad surgical risks and what in general I call the "bad starters". Many of them do unexpectedly well but if we aim at a resectability rate of 90% or over, there is bound to be a high proportion of late cases; this is shown in my series by the fact that the C cases considerably outnumber the A and B cases combined (Table III).

Even the Stage IV cases with secondaries in the liver do well for a variable number of months and no statistics can measure the relief that we give to these cases. In my series of perineo-abdominal excisions there have been 53 Stage IV cases in the last ten years, with only 1 operative death, and 11 have survived for two years or more.

Estimation of operability.—I hesitate to label any case of cancer of the rectum as inoperable except when the patient is moribund from old age, severe general disease or massive liver metastases with jaundice. The term "borderline operability" is a better one to use, and after preparation many turn out to be more mobile and better subjects for operation than the first estimate would suggest.

Age.—Advanced age does not in itself contra-indicate a radical operation and in the last ten years I have done a perineo-abdominal excision in 171 patients of 70 or over, in fact they constitute more than one-quarter of the total operated upon during this period (Table I). 14 patients were 80 or over, the three oldest being 84, 85 and 86, and all 3 recovered.

Table I.—One-stage Perineo-abdominal Excision for Malignant Disease of the Rectum and Anal Canal

Operation Mortality Since 1932

Total Series = 1,223 Cases

Period	No. of cases	Operative deaths	Operation mortality %
1932–36	81	21	26
1937–46	517	58	11
1947–56	625	33	5·3
Total	1,223	112	9·2

This is my total series since 1932 comprising all hospitals and clinics. Both radical and palliative cases are included.

In the last ten-year period, 1947–56, the operation mortality in 625 cases has been 5·3%. Included in these 625 cases are 422 done at St. Mark's Hospital with 11 deaths =2·6%. The operation mortality in the remainder (203 cases) done elsewhere than at St. Mark's was 22 deaths = 10·8%.

Nutritional state.—Since the end of the last war we have all become accustomed to operate on obese subjects and with modern care they usually do well. The grossly obese subject, by which I mean the patient weighing 16 st. or more, should have special consideration and occasionally it may be advisable to postpone operation for four to six weeks while the patient is put on to a drastic slimming regime: a biopsy report of an average or low grade malignancy would favour such a course.

Full medical investigation.—This is now routine in all cases and involves investigation of the blood picture, blood urea, X-ray of chest, ECG and medical opinion; it should be carried out in good as well as in bad risk subjects. An X-ray of the chest which proves lung metastases to be present is sometimes the deciding factor against laparotomy in an advanced case of doubtful operability or one with clinical evidence of secondaries in the liver.

I used to be apprehensive about patients with calcified aortic disease but as long as all the facts are known and the surgical team appreciates the importance of maintaining the blood pressure at operation these cases can be brought to a successful conclusion.

In the bad-risk patient the physician's opinion as to preliminary and subsequent supportive treatment is of great importance in reducing the surgical risk. I and all my colleagues at St. Mark's are grateful for the help and guidance we have received for many years from Dr. Courtenay Evans. If he advises me to pause for a week or two before embarking on a major operation I take his advice and the patient eventually comes to operation in a much better state.

Biopsy.—I attach the greatest importance to a preliminary biopsy and regard this as essential. Biopsy enables the granulomatous lesions, such as those due to amœbic dysentery and tuberculosis, to be differentiated from carcinoma. Lately I have had a case of generalized lymphosarcoma with ulcerated rectal lesions which exactly resembled a carcinoma clinically, but this was correctly identified by biopsy thus enabling the patient to be referred for deep X-ray therapy. Biopsy usually enables the high-grade and colloid lesions to be diagnosed. I think it is correct to say that biopsy is reliable in close on 100%; in the paper published by Dukes, Bussey and myself (Gabriel *et al.*, 1951) in a series of 670 cases we proved biopsy to be correct in 97%. It is only in the case of large villous tumours covering many square inches that one cannot expect a biopsy infallibly to reveal a small focus of carcinoma and then the clinical signs of friability, ulceration and induration are the decisive factors.

Examination under anæsthesia (E.U.A.).—This is a good line to adopt in the case of a deeply ulcerated carcinoma of the lower third of the rectum especially when it involves the anal canal, for if it is situated posteriorly it may be impossible otherwise to get fragments for biopsy. E.U.A. is useful when a male patient has a deeply ulcerated growth anteriorly and it is important to decide if the prostate is invaded or not. A stricture of the rectum or anal canal may also be an important indication for examination under anæsthesia if symptoms suspicious of a rectal carcinoma develop.

Barium enema.—This is not necessary or routine practice in the average rectal carcinoma and, in fact, a barium enema given to a patient with a stenosing rectosigmoid growth might precipitate an attack of obstruction. I quite frequently see patients who have had a barium enema when there is a growth within easy reach of the finger and sigmoidoscope; however, sometimes these films show points of interest such as a short pelvic colon or advanced diverticulitis.

Points in Operative Technique

The operation has been described elsewhere (Gabriel, 1948) and I need only mention a few special points. Sulphonamide preparation is not given as a routine and is reserved for the occasional patient with noticeably offensive diarrhœa and those with a deeply ulcerated growth which might perhaps become perforated in the course of the operation.

A right paramedian incision is used for the preliminary exploration and is, I think, better than a left-sided incision because it will be farther from the colostomy.

After opening the peritoneal cavity a quick infiltration of the abdominal wall is done with 1% procaine. The liver, the rest of the colon and the pelvis are examined. If the growth is advanced anteriorly it is often helpful in the male to make a transverse incision with a long-handled scalpel at the bottom of the rectovesical pouch and a tentative separation can be made in the plane of cleavage between the rectum and the base of the bladder. The same manœuvre is useful in the female especially when a hysterectomy has been done previously and it might be difficult to find the peritoneal cavity from below.

After deciding that the growth is operable the pelvic colon is held out by an assistant and the base of the pelvic mesocolon is injected with 10 c.c. of 1% procaine without adrenaline. This effects a block of the inferior mesenteric plexus and must be to the patient's advantage in preventing ascending impulses. Many of these patients leave the table with a pulse-rate of 70 to 80.

The abdominal wound is closed temporarily with 4 or 5 through-and-through sutures tied over gauze and the perineal phase is then carried out in the left lateral position. The dissection is done with straight scissors exactly as it used to be done by my old chief, J. P. Lockhart-Mummery. The peritoneum is opened widely and is cut upwards on each side as far as can be reached with long blunt-ended scissors. The lateral ligaments are cut and ligated if necessary. If there is any suggestion of lateral spread the middle hæmorrhoidal pedicle can be dissected laterally for a short distance and can be divided if thought advisable by cutting diathermy.

The fully mobilized rectum encased in a sterile glove is washed with saline and pushed up into the abdomen. Sometimes in the case of a large growth in a small pelvis the mobilized rectum has to be left in the pelvis and is brought upwards when the abdomen is reopened. The stitch closing the pelvic floor is usually started from below as suggested by F. W. Connaughton many years ago and the needle is passed up into the abdominal cavity on a piece of gauze with the excess catgut wrapped round it.

The main pedicle is usually ligated above the first sigmoid branch. I do not believe in the "high tie" technique unless there is some specific indication for this which in my experience is rare.

A left iliac colostomy is established, with closure of the lateral space as an invariable routine. The pelvic floor is easily closed by bringing up and then carrying on the stitch

which has been started from below. A steep Trendelenburg tilt is not required and in fact a 15-degree tilt is seldom exceeded. The internal oblique is sutured to the side of the mesocolon and colon to prevent prolapse of small intestine. A snip with scissors through the fibrous margins of the external oblique serves to prevent any undue compression of the colon. The bowel is divided with a cautery about 4 cm. external to the abdominal wall and is decompressed by a soft catheter. Dry gauze dressings are anchored round the colostomy with Michel clips.

Results

When one meets with an ulcerated flat malignant growth at or about the level of the ano-rectal ring it is impossible, I think, on clinical grounds alone to say if it is a carcinoma of the rectum invading the anal canal, or a carcinoma of the anal canal extending up to or beneath the rectal mucosa. In any case the histology of these tumours is extremely difficult, they may be of mixed histology, part squamous and part adenocarcinoma, so that a biopsy is not absolutely final. The one fact that usually applies is that in this situation a carcinoma is of a high grade of malignancy and the outlook is fairly bad whatever the histology shows. I think these tumours, speaking generally, should be ranked as carcinomas of the rectum (Fig. 1A, B, C, D).

The problem is obvious and it would be a pity to split up a series of cases into small sections on a basis of histology. I cannot see that the surgical risk differs at all and from the point of view of statistics the larger they are the more accurate and informative they are likely to be.

The figures which I present include 15 squamous carcinomas of the anal canal, 1 squamous carcinoma of the rectal ampulla, 5 sarcomas of the rectum (one being in conjunction with an adenocarcinoma), 1 melanoma, 3 mixed adenocarcinoma and squamous carcinoma, and 1 malignant carcinoid with liver secondaries. These cases are included in my mortality figures and 20 that were operated upon before December 31, 1951, are shown in the survival rate (Table III).

Table I shows the steady drop in mortality and in the last ten years my overall mortality has been 5·3%. During this time the death-rate in my patients at St. Mark's Hospital has dropped in the five-year period 1947–51 to 3·6%, and from 1952–56 to 1·5%. At one time I had 168 cases without a death, and during the ten years 1947–1956 my mortality at St. Mark's in 422 cases has been 11 deaths = 2·6% (Table II).

Table II.—St. Mark's Hospital

One-Stage Perineo-abdominal Excision of the Rectum for Malignant Disease of the Rectum and Anal Canal, Radical and Palliative

For the ten-year period, 1947–1956 inclusive (W. B. Gabriel)

Period	No. of cases	Operative deaths	Operation mortality %
1947–51	223	8	3·6
1952–56	199	3	1·5
Total	422	11	2·6

In the last five years 73 patients were 70 or over, 5 being over 80. At one time there were 168 consecutive cases without a death. The 3 operative fatalities since 1952 were: (1) a frail old man aged 80 who died on the second day after operation from cerebral thrombosis and coronary disease; (2) a frail senile man aged 77 who died of cardiac failure on the fifth post-operative day; and (3) an immensely broad short man aged 65 who died from hæmorrhage, shock and coronary disease three hours after operation.

The mortality rate of my patients outside St. Mark's has been much higher, amounting to 22 deaths in 203 operations (10·8%). The majority of these were done in the Royal Northern Hospital, there being 183 perineo-abdominal excisions with 21 deaths = 11·5%. This is more than four times the death-rate in St. Mark's Hospital in the corresponding period and is a serious and significant difference. There are probably a number of factors which account for this: on the one hand we have St. Mark's with its highly specialized team and the intake of carcinomas is increased by the patients admitted to our private wards; these usually provide earlier cases and better operative risks, whereas in a big general hospital I believe we see a higher proportion of older and advanced cases. This is borne out by the fact that 1 in 10 of my Royal Northern cases (18 out of 183) have been

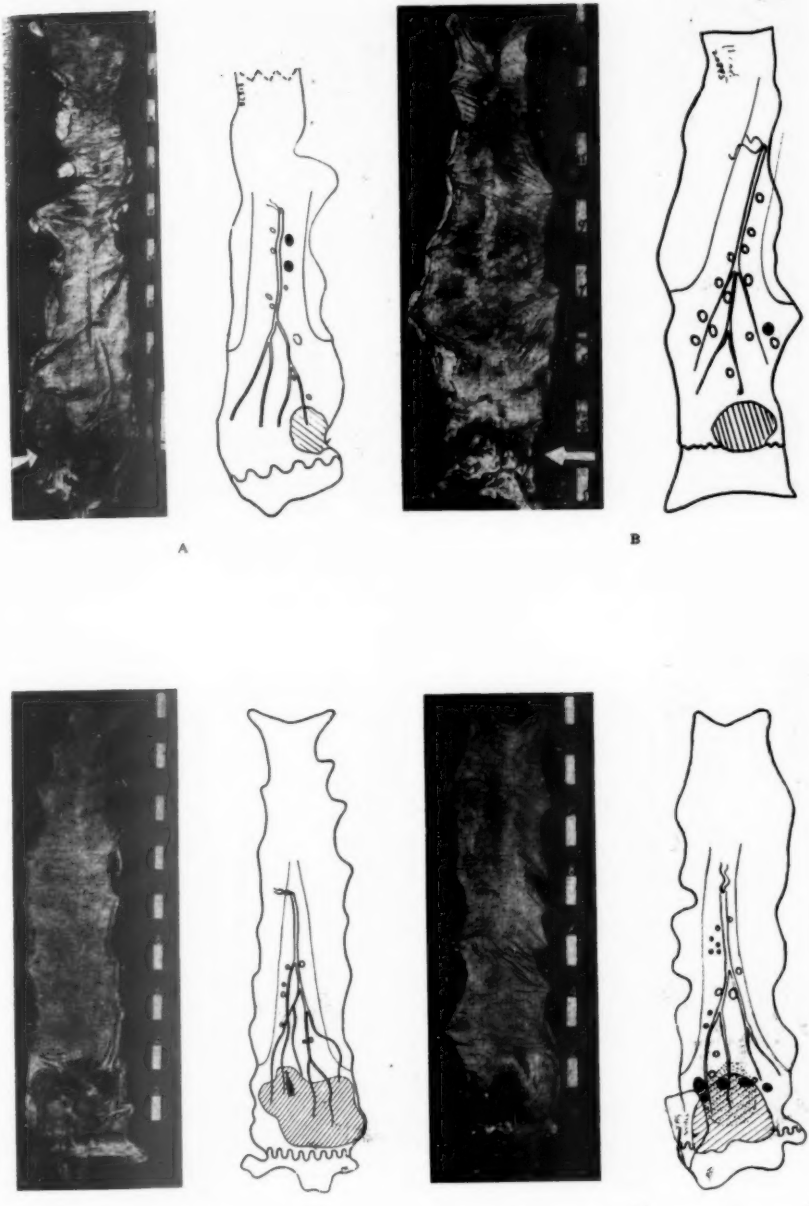


FIG. 1.—Figure showing lesions of different histological types involving the lower third of the rectum and anal canal. A, Adenocarcinoma of lower third of rectum invading anal canal. B, High-grade squamous carcinoma of anal canal extending up into the rectum with metastases in one hæmorrhoidal lymph node. C, Mixed adenocarcinoma of rectum and anaplastic squamous carcinoma of anal canal. This patient has survived for twelve years after a perineo-abdominal excision. D, Anaplastic carcinoma of anal canal. This was originally considered to be anaplastic squamous, but on review it is now believed to be anaplastic adenocarcinoma.

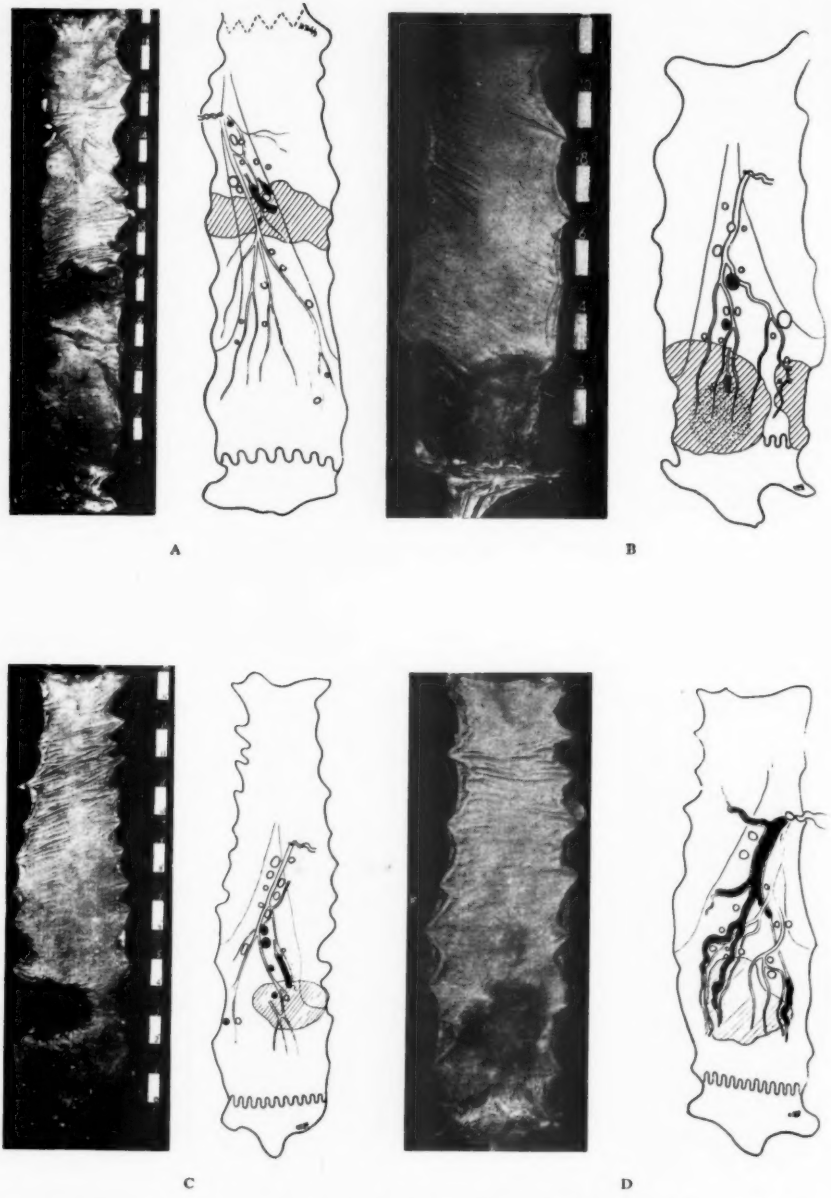


FIG. 2.—Four cases of cancer of the rectum with proved venous involvement followed by long survival after perineo-abdominal excision of the rectum.

A.—C2 case survived 8 years.
B.—C1 case survives 12¾ years.
C.—C1 colloid case survives 17 years.
D.—B case with extensive venous involvement to the point of ligation of the pedicle. This patient is alive and well 20 years after operation.

Stage IV cases with secondaries in the liver and of the C cases more than one-quarter (23 out of 88) proved to be C2 cases.

Furthermore I have formed the opinion that these patients do not do so well when nursed in big busy general wards. At St. Mark's we have, I believe, a higher ratio of nurses to patients than in most London hospitals. My figures indicate the advantage of doing these operations in special clinics or wards.

Survival Rate

This is shown in Table III which includes all operation survivors from 1932 to December 31, 1951, so that a clear period of five years has elapsed. Both radical and palliative cases are included and the difference in survival rate in the A, B and C groups follows the usual pattern.

Table III.—Five-year Survival Rate Following Perineo-abdominal Excision of the Rectum for Malignant Disease of the Rectum and Anal Canal
(Comprising all cases operated upon from January 1932 to December 31, 1951)

Group	No. of operation survivors	Untraced	Died of other causes in less than five years	Died of cancer in less than five years	Alive at five years	Percentage of five-year survivors
A	117	1	9	7	100	85
B	281	0	29	72	180	64
C	453	1	26	276	150	33
Total	851	2	64	355	430	50·5

Note.—This list includes 5 B cases and 27 C cases who were proved at operation to have liver metastases, that is, they were Stage IV cases. Other palliative operations due to irremovable local spread are also included in this series.

If the Stage IV cases are deleted the survival rate in B cases is improved to 65% and in C cases to 35%.

Of the 2 untraced cases 1 was operated upon in Spain and the other has emigrated to Southern Rhodesia.

If the Stage IV cases with secondaries in the liver at the time of operation are excluded (5 B cases and 27 C cases) the survival rate in B and C cases is slightly improved to 65% and 35% respectively.

Before concluding there is one point to which I must refer. I have heard the perineo-abdominal method criticized on the score that venous embolism is more likely to take place than in the other methods of combined excision.

I do not think this is a just or valid argument. My series is bound to contain the average number of cases of venous involvement and my survival rate figures speak for themselves. This operation depends for success, like any other, on the operator's technique and gentleness. The method of dissection of excised specimens which has been employed at St. Mark's for many years enables the cases of venous involvement to be detected with fair certainty and the examples of venous involvement followed by long survival (Fig. 2A, B, C, D) show that this does not necessarily imply that embolism to the liver must take place either before or during operation.

This series is probably unique in that of the 1,223 cases reported, all except one were examined and classified by Dr. C. Dukes at St. Mark's Hospital, and to him and his department I am supremely grateful.

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Mr. O. V. Lloyd-Davies:

Synchronous Combined Excision

The operation of synchronous combined excision, requiring as it does two surgeons, can only be carried out in the lithotomy-Trendelenburg position. Bloodgood in 1906 described the use of Halsted's perineal board or table (*see* Halsted, 1924), upon which the patient was moved during the operation from Trendelenburg to lithotomy position and Clogg in 1923 described a rather similar procedure. Mayo in 1910 advocated the lithotomy position for perineal excision and there is little doubt that the even spread of the buttocks and the four-square approach to perineum facilitates the dissection from this aspect.

The position more or less as used to-day was first described by Kirschner in 1934 and Devine in 1937.

We first used the position at St. Mark's in 1936 for abdomino-anal resections and in 1938 Naunton Morgan and I did the first synchronous combined excision. It was a case I well remember with extensive involvement of the iliac and obturator lymph nodes but unfortunately our efforts were of no lasting benefit to the patient. It did, however, reveal to us what could be done in those days without increasing the operative mortality.

Since that time as the result of team work the positioning of the patient has been gradually perfected.

The Goligher sacral rest to elevate the perineum has replaced the sand-bag. A small lumbar air cushion made by Lilo eliminates undue kyphosis. The Frankis Evans epaulette shoulder-rests have removed any danger of a brachial palsy and the angled leg-rests have been modified to extend the thighs more fully to give an even better access to the abdomen.

The lithotomy-Trendelenburg position has many advantages. *In the first place* the choice of several operations is available without change in the patient's position. The single surgeon may carry out either an abdomino-perineal or perineo-abdominal type of excision according to his inclination. Between a quarter and a third of the cases seen may be suitable for some form of restorative resection—either an abdomino-anal or anterior resection. This position is essential for these operations in order to carry out the special rectal toilet before rectal division to eliminate the possibility of transplantation of free cancer cells in the lumen.

Briefly, it consists of irrigation through the anus of the portion of rectum to be retained after an exclusion clamp has been placed across the rectum at a minimum distance of 5 cm. below the lower margin of the tumour. The solution used is 1 : 500 perchloride of mercury. The proximal colon is also very carefully swabbed out with the same solution and suture-line recurrences have been virtually eliminated by this method.

In Hartmann's operation, now less commonly used than in the past, this rectal toilet is also very necessary and can only be accomplished in the lithotomy-Trendelenburg position.

Secondly, in restorative operations a second assistant can be very conveniently placed between the extended legs.

Thirdly, where the bladder may be incompletely emptied by preliminary decompression, complete emptying can be readily obtained with virtually no disturbance to the general towel arrangement.

Fourthly, any further examination such as cystoscopy, ureteric catheterization or a sigmoidoscopy when searching for colon polyps, may all be accomplished during a laparotomy with the minimum of disturbance.

Regarding the virtues of the synchronous method, there can be no doubt that it has influenced the resectability rate although other factors such as advancements in anæsthesia and the fuller understanding of the pre- and post-operative care of the patient together with an increase in our knowledge of electrolytic balance have also played a considerable part.

At St. Mark's Hospital the resectability rate has increased from 60% to over 90% since 1938 and from information I have obtained from hospitals elsewhere in the country where this method is used the resectability rate has in many instances been doubled.

In the straightforward case the operation is of course time-saving but it also allows those patients with large bulky tumours or with a frozen pelvis—frozen as often as not by inflammatory tissue—to be given a chance. They are often the cases in which removal of the rectum can only be accomplished by a dual approach and the end-results of operations of such magnitude are often very gratifying and certainly worth while.

In 14·6% of our cases other adherent organs have been removed with the rectum, such as loops of ileum, the uterus and adnexa, the vesicles and portions of the prostate and bladder—again with considerable time saving when these additional structures require removal. In these advanced cases the crude five-year survival rate is 25%—a low figure—but it does indicate that these extended operations have been worth while.

The figure of 14·6% does not include the removal of the posterior vaginal wall which has for some years been a routine procedure for any tumour in the lower half of the rectum whether clinically adherent to the vagina or not—with the result that a vaginal recurrence is now a rarity. Where even more extensive excisions such as pelvic exenteration are necessary most surgeons agree that the synchronous operation using the lithotomy-Trendelenburg position is the method of choice.

The C2 case, that is the case with glandular spread up to the highest point of ligature, presents a problem. If it were possible to convert a C2 case into a C1 case by doing a higher ligation—that is by tying the inferior mesenteric trunk at its origin—it might eventually be possible to show that there was an actual prolongation of life as the result of this step. There are, however, many other factors.

Although high ligation is an almost routine procedure at St. Mark's for upper-third, rectosigmoid and left colon tumours, in this series which mainly concerns tumours of the lower and middle thirds it was not done as a routine, but it should certainly be considered in those cases with palpable glands reaching the promontory. In poor-risk cases or those with marked arteriosclerosis or those where fat obscures the vascular anatomy, this extended operation would be unwise and might well increase the operative mortality.

There are other useful features in the synchronous operation which should be mentioned—such as the dual control of hæmostasis. Ligatures may be very conveniently passed up or down the empty pelvis and tied by the surgeon most conveniently placed. The pelvic peritoneal floor closure over an empty pelvis is a great advantage in itself and allows a wider removal of peritoneum and subperitoneal tissues.

Finally the synchronous operation is ideally suited for the training of the young surgeon in rectal dissection—since one part of the operation can be completed by a trained surgeon whilst the other instructs a junior. In this way there is the minimum loss of time and the safety of the patient is not impaired.

From 1938 to 1955—1,090 synchronous combined excisions have been carried out at St. Mark's Hospital. These have been operated upon by the beginners and the experienced.

The resectability rate which for some years now has been well over 90% obviously includes an increased number of poor-risk cases—but despite this the overall operative mortality for the series which includes both palliative and radical cases is 8·6%.

There has been a steady decline in this rate from 11·5% in the first five-year period to 4·4% in the last period. The crude five-year survival rate for radical cases is 53·4% but this figure cannot be compared with any other combined series for, since 1948, one-quarter of the cases presented for this operation have had restorative resections. This quarter represents the cream of the tumours in the upper half of the rectum and analysis of this group shows an increased proportion of early cases with a reduced operation mortality rate, and a much increased survival rate.

From another aspect they are not comparable even with Mr. Gabriel's perineo-abdominal figures at St. Mark's since more patients of the older age groups are included in this series, the average age of both males and females is nearly two years older. This makes quite a difference when the crude five-year rate is statistically corrected for age.

Some comparisons can be made with the perineo-abdominal method, and of those that are important urinary retention and infection should be mentioned. This is two and a half times more common in synchronous excisions and the cause in the majority of cases is due to varying degrees of damage to the nervi erigentes.

Watson and Innes Williams (1952) were of the opinion that this damage resulted from a failure to divide Waldeyer's fascia posteriorly. I find this explanation difficult to accept since the division of this fascia at the bony pelvic outlet is a formal and defined step in the perineal dissection. A truer explanation probably lies in the comparison of these two operations. When the major part of the dissection is carried out from above as in the synchronous or abdomino-perineal method, the ureters can be seen and, if necessary, exposed throughout their course. This enables the surgeon to remove the lateral ligaments widely out upon the pelvic walls and this I think is where the nerve damage occurs. When the major part of the dissection is carried out from below, as in the perineo-abdominal method, the surgeon has no accurate knowledge of the position of the ureters and takes a course closer to the bowel.

Goligher in 1951 reported upon the sex function after combined excision and found one-quarter to be totally impotent. There was no statistical difference between the synchronous and perineo-abdominal operations but the series was really not large enough to evaluate.

When dealing with malignant disease it is very necessary to be as radical as possible but one should balance the effects of any complication in terms of the length of the patient's life. At present there are no figures to give us any decision in this matter.

From a practical viewpoint I think the perineo-abdominal method of dissection is the operation of choice for the case of colitis where the patient is often young and any increased

risk of the destruction of sex function or a urinary disability would be totally unwarrante[d]. It may also well be the method of choice for the very elderly man with prostatic symptom[s].

One final comparison relating to pulmonary embolism. It has been suggested that th[e] position of the calves of the patient in the leg rests might induce increased venous stasi[s]. The legs are, of course, well elevated during periods of the synchronous operation and th[e] St. Mark's statistics show no difference in the incidence of embolism between the perineo-abdominal and synchronous methods.

I have tried to give a fair assessment of the synchronous combined excision method bu[t] there is undoubtedly a place for all these operations in the hands of those well skilled i[n] the various methods.

The synchronous operation has now a well-established position in the surgery of rectal cancer and is becoming increasingly the method of choice. In the average case there can be no difference between the results of the three established methods of rectal excision. However, in the advanced cases, bulky and adherent to the pelvis or to other organs, this may often be the only method by which excision is possible and some good results can be obtained.

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Mr. C. Naunton Morgan:

Restorative Resection

In considering the subject of carcinoma of the rectum re-evaluation of the mode of lymphatic spread has shown that although the upward pathway is by far the most constant and frequent, downward spread is uncommon. Dukes has shown that retrograde lymphatic involvement was present in 6·5% of 1,500 operation specimens, but in only 2% did this occur for more than 2 cm. It was also noted in those specimens exhibiting downward extension that about three-quarters of the growths were of a high grade of malignancy. Lateral spread in the pelvic fascia and musculature is also unusual when the rectal carcinoma lies above the pelvic peritoneal pouch (Wood and Wilkie, 1933; Sauer and Bacon, 1951). In fact, local recurrence following combined excision of growths with lymphatic involvement, situated above the peritoneal cul de sac, was found in 3·6%. With similar lesions placed below this level, the incidence of local recurrence was much higher, namely 23% (Gilchrist and David, 1948). These facts have resulted in renewed attempts, in selected cases, to preserve a portion of the rectum and anal canal and to restore continuity.

The proportion of growths suitable for such procedures is small when compared with those for which combined excision is essential. For this reason, in order to present a true picture of the place of restorative methods, it is desirable to record personal experience in the treatment of all carcinomas of the rectum, more especially in recent years. The role of restoration will thus be seen against the broad background of the most radical of all operations for rectal carcinoma, namely combined excision. Since many cancers situated in the rectosigmoid region have, in the past, often been removed by combined excision, growths at this site are included in the present series of carcinoma of the rectum. The level of the lower border of the sacral promontory has been arbitrarily used to mark this site.

Operability (resectability) rate.—Of the total number of carcinomas of the rectum seen, 94·8% were removed.

Operative mortality rate.—After exclusion of 54 major operations performed by my colleagues on my behalf and 19 local excisions performed for tiny growths and malignant polyps, some 523 major operations remain. Non-restorative operations numbered 381 of which 361 were combined excisions and the remaining 142 (27%) restorative procedures. The operative mortality rate for synchronous combined excision and restorative resection is the same, namely 4·2%. These figures cover the period 1948–1956.

Criteria for Restorative Operations

At St. Mark's Hospital we have formulated certain criteria for the selection of cases suitable for restoration of continuity.

(*a*) *Type of operation.*—The operative procedure must allow of normal defæcation. Thus the anal canal with its musculature and linings should be left undamaged together with a portion of the rectum above the ano-rectal ring. The rectum and a portion of the sigmoid colon together with the meso-sigmoid and meso-rectum must be excised *en bloc* for a distance of at least 5 cm. by measurement, below the lowest border of the growth. The same upward lymphatic field as that required for radical combined excision should be removed.

Both anterior resection and abdomino-anal resection (Maunsell-Weir) satisfy these requirements but the latter operation does not always give a perfect functional result. Further, in order to restore continuity, a long sigmoid loop or mobilization of the transverse colon is necessary. Of the 142 restorative operations the large majority, 138, were anterior resections.

(*b*) *Site.*—The lesion should not be less than 10 cm. from the anus by sigmoidoscopic measurement and in addition should not lie below the level of the peritoneal reflection. The peritoneal reflection is variable, but the sigmoidoscopic measurement *together with* the relation of the growth to the peritoneal reflection form a useful yardstick for assessing the site of a growth.

(*c*) *Extent and grade.*—When the primary growth is advanced with evidence of marked extra-rectal or peritoneal spread, or is of a high grade of malignancy, the chance of local recurrence is great. Under these circumstances a restorative operation should not be undertaken. However, when there are a few secondary deposits in the liver, if complete removal of the primary growth is possible, then restorative operation is desirable. In fact, apart from cases in which the primary growth is extensive and liver secondaries are judged not to occupy more than half the liver substance, restorative resection is the best palliative operation. Of the 138 anterior resections in this series 28, or 20%, were palliative in nature.

(*d*) *Build of the patient.*—Owing to operative difficulties and inability to define the mesenteric vascular pattern, a short obese subject with a small pelvis and fat-laden mesentery is generally unsuited to restorative operation.

Implantation of Malignant Cells

Recurrence in the suture line or in the vicinity of the anastomosis following anterior resection was noted in a restorative resection I performed in 1936. This necessitated combined excision about six months later. The risk of implantation of growth at operation was then clearly demonstrated and in 1950, Lloyd-Davies and I recorded the gravity of this hazard. Goligher *et al.* (1951) reported that transplantation of growth accounted for about 50% of recurrences at or near the suture line.

That malignant cells can be implanted into the colonic suture in rabbits was shown by Vink (1954) especially after "sterilization" of the bowel by locally acting sulphonamides and streptomycin. McGrew *et al.* (1954) reported the presence of free malignant cells in the colon in 42% of proximal ends and 65% of distal ends of resected large intestine.

At St. Mark's Hospital, since 1948, we have attempted to destroy malignant cells in the lumen of the bowel by exclusion of the bowel 5 cm. below the growth followed by thorough lavage of the rectum with 1 : 500 mercury perchloride. The rectum is then divided below the clamp. The proximal divided end of the colon is swabbed with the same solution and particular attention is given to the cut ends of the bowel to be anastomosed.

Since using this technique the local recurrence rate in the region of the anastomosis has fallen from 21% to 1·5% in the last 136 operations. It is admitted that the two series are not strictly comparable since as yet enough time has not elapsed—but these figures are strongly suggestive.

In one of the two cases with local recurrence, the exclusion clamp slipped during removal of the specimen and the other was an advanced growth with glands extending high on the aorta.

Anterior Resection—Results of Treatment

The number of abdomino-anal resections performed was only 4 and for this reason only the 138 anterior resections will be considered. The operative mortality rate for anterior resections performed at St. Mark's Hospital was 2·5% and at other hospitals was 7%.

Likewise the mortality rate for synchronous combined excisions was 3·3% but was 5·2% in cases treated elsewhere. The influence of sex on the operative mortality is noteworthy. In the male undergoing anterior resection, it was 6·6% whilst in the female only 1·6%. The mortality rate following synchronous combined excision in males was 4·2% and in females 3·3%.

Survival rate.—Dr. Cuthbert Dukes has already discussed the fallacies of comparison of results without taking into account the age and sex of the patient, and the site, extent and histological grading of the growth.

To illustrate this point the crude five-year survival rate following 138 anterior resections between 1948 and 1956 was 54%, whilst that of 361 synchronous combined excision was 46%. This is to be expected since the less advanced growths have, in the main, been subjected to anterior resection. In fact, the number of early or A cases treated by anterior resection was over twice as many as those undergoing combined excision. The survival rate in the female is also better than in the male (males 54·6%, females 79·9%), but these are figures for "radical cases" only.

A reasonable comparison of the results of operations can only be obtained by considering the radical treatment of growths at similar sites, in this instance in the intraperitoneal rectum and rectosigmoid after correction for age, sex and extent of the growth.

The crude five-year survival rate for 110 *radical* anterior resections has been shown to be 66%. When this figure has been corrected, the survival rate is 81%. A similar corrected survival rate for a comparable group of growths removed by combined excision is 78·5%.

The slight difference is not of statistical significance but it does support the view that anterior restorative resection has a place in the treatment of suitable growths of the upper rectum and rectosigmoid and that patients so treated have as good a prognosis, without a colostomy, as those subjected to combined excision.

We have all been anxious about the wisdom of performing restorative operations. It is now felt that it has been proved beyond all doubt that anterior resection has a place in the treatment of carcinoma of the rectum and the results compare favourably with those of combined excision. This is shown in the happiness and gratitude of patients alive and well without colostomies.

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Section of Obstetrics and Gynæcology

President—R. A. BREWS, M.D., M.S., F.R.C.S., F.R.C.O.G.

[*June* 28, 1957]

Medico-legal Adventures and Misadventures in Gynæcology and Obstetrics [*Abridged*]

By F. E. CAMPS, M.D., D.T.M.&H.

THOSE who practise forensic pathology must encounter other important aspects of gynæcology and obstetrics than those associated with crime. In fact, the most common criminal aspect of the subject—criminal abortion—is almost always due to a "lay" operator.

Thus, apart from deaths from violence or criminal abortion, the Coroner investigates those associated with surgical operations, therapeutic procedures, and, for this may not be generally appreciated, deaths in which the public interest is involved such as food poisoning. Into such a category will fall, when associated with mortality, outbreaks of puerperal infection and of infections of babies both newborn and in the neonatal period.

Before the introduction of chemotherapy and antibiotics, streptococcal infections were of considerable interest to the epidemiologist, and following the judgment in the case of Lindsay County Council *v.* Marshall (1937) there was an added medico-legal flavour in respect of the liability of maternity units when puerperal infection occurred. It is of interest to notice that twenty years later this case has apparently been forgotten, whether due to a more modern outlook or as a result of the National Health Service.

Clearly the investigation of multiple or recurrent cases of infection in any community, whether it be small or large, is an epidemiological matter, but the investigation must be undertaken with the full co-operation of everybody whether it be a trainee or a consultant, a technician or a pathologist or even a police officer. Apart from ethical considerations, there is always the overwhelming opinion in this country that it is better to deal with such matters in public.

In addition, all unexpected or sudden deaths following midwifery or gynæcological procedures should be within the range of the Coroner's investigation.

Examples of the scope of his investigations can be given under the following headings:

1. *Deaths During or Following Operation or Delivery*

Into this category fall such things as hæmorrhage following operation and post-operative shock. In many of such cases, death appeared to be inevitable but operation essential to give any chance of life. Clearly it is against public policy for surgeons to be prevented from embarking upon forlorn hopes. At the same time, it is advisable when risks deliberately taken do not succeed that the public's mind should be relieved of any suspicion that *death was, in fact, inevitable*. For this reason the Coroner may decide to employ a pathologist, not associated with the hospital or surgeon, to carry out the autopsy. Indeed the hospital pathologist frequently desires to be relieved of the responsibility of having to criticize a colleague. In any event, there should be no reason to expect the standard of autopsy to be inferior to that done in hospital or that all necessary material for investigation should not be collected.

It is of interest in connexion with delivery, that whereas prior to 1939 deaths from obstetric shock associated with the premature administration of preparations of pituitary extracts were relatively common, I have seen none for the last three years. This may be because I no longer work in rural areas. Among other causes of death during or after delivery are those due to cardiac inhibition of which the following is an illustrative case:

"A young woman (primipara) had her baby in hospital and it was necessary to do an episiotomy. In order to make her as comfortable as possible—she was a doctor's wife—

the obstetrician suggested an immediate repair. This was performed under light anæsthesia in the form of trilene, gas and oxygen. When the needle entered the perineum her heart stopped and nothing restored it."

Such a case fulfils all the criteria demanded:

(1) *a state of sensitivity*—light anæsthesia.
(2) *a stimulus* —needle prick.

Such a case is similar to those believed to occur during criminal abortion, when the woman is very frightened. It may be, however, that some of those described by pathologists were, in fact, due to other causes.

From time to time, cases are seen which have died at home or shortly after arrival in hospital from concealed accidental hæmorrhage, while others still die, but not commonly, of post-partum hæmorrhage. Such deaths may be complicated by blood transfusion and it may be difficult to assess how much the death was due to hæmorrhage or to some miscarriage of the transfusion. It is also clear that women who die during labour (other than from some obvious vascular disease) require a most careful and critical autopsy: during the last year I have seen a fatal embolism due to liquor amnii.

II. *Deaths During Gynæcological Procedures*

Deaths occurring during therapeutic procedures are rare although the hazards of blood transfusion should always be borne in mind. Only one case of air embolus has been encountered following insufflation of the fallopian tubes for investigation of sterility. In this case the air entered because of rupture of adhesions at the distal end of the right fallopian tube due to an old ectopic gestation.

III. *Injuries to the Genital Tract Due to Other Procedures*

Occasionally, gynæcological complications arise from other procedures and in 1956 there was a somewhat unusual case:

"A married woman of 56 without children was admitted to hospital on account of an anæmia. Examination of the fæces showed persistent occult blood and as the source could not be discovered a barium enema was requested to exclude malignant disease. The technique employed was the insertion of a catheter with an inflatable balloon and the subsequent introduction of barium under gravity pressure. The examination which was carried out in semi-darkness appeared to proceed properly although the woman showed signs of discomfort which were regarded as normal. Radiological examination showed what appeared to be an obstruction and she was allowed to follow the usual routine of emptying the bowel in a bedpan and removal of the catheter. This was accompanied by passage of a little blood which did not give cause for alarm and she returned to the ward apparently a little shocked. On the following morning she complained of abdominal pain and a further radiological examination showed free barium in the peritoneal cavity. A laparotomy confirmed this and a colostomy was performed as it was believed that she had perforated a large bowel growth. As there was bleeding from the vagina, an apparently intact hymen was incised which revealed a tear in the vaginal wall about 1½ in. long. In spite of active treatment including blood transfusion she died eight hours after the operation.

"Autopsy revealed an extravasation of blood extra-peritoneally in the loose pelvic tissues which had arisen from vertical tears in the lateral walls of the vagina, typical of overstretching; barium was present in the tissues beneath. It was also present in the peritoneal cavity and the route of entry could be traced through the uterine cavity and fallopian tubes. It was therefore quite clear that the barium had, in fact, been introduced with the catheter and balloon in the vagina, the vaginal tears being due to distension by the balloon and the barium to gravity pressure with the introitus blocked by the balloon."

IV. *Coincidental Findings at Autopsy*

From time to time, coincidental gynæcological and obstetric findings are revealed during routine medico-legal autopsies and perhaps the most interesting was a three months' pregnancy with a butterfly pessary still in situ in a woman who had taken her life by coal gas poisoning.

V *Deaths Due to Abortion or Attempted Abortion*

Abortions are the most common cause of investigation and most of these are suspected if not proved to be due to interference. Apart from death from shock, air embolism, hæmorrhage or cardiac inhibition, the commonest cause of death is infection. The infecting organism has changed during the last twenty years, mostly due to the introduction of antibiotics. Although anaerobics, streptococci and staphylococci are occasionally

encountered with broad ligament infection and pyæmia, the commonest organism is *Cl. welchii*. Death may occur in two ways, either rapidly from septicæmia, in which case the external appearance of the body is usually leaden in colour with slight jaundice and autopsy reveals a gross blood-stream infection, or later from renal failure with the incorrectly-called "lower nephron nephrosis". Those due to an obvious clostridial infection present no difficulty but it is not uncommon to find renal failure with a similar picture with or without gangrene or necrosis of the uterine wall without isolation of a specific organism. It seems probable that in some of the cases the renal condition is consequent upon antiseptic fluid entering the blood stream through the placental sinuses during its introduction into the cavity with intent to cause abortion.

VI. *Other Criminal Acts*

Recently a prosecution was carried out under the Infant Life (Preservation) Act 1929. This Act provides that any person who *with intent to destroy the life* of a child *capable of being born alive, by any wilful act* causes a child to die *before it has an existence independent of its* mother shall be guilty . . .

In this case, the child believed at ante-natal examination to be of 26 weeks' gestation, was delivered on the day following an assault during which the mother was struck or kicked on the abdomen. The fœtal heart was heard on admission to hospital but not the following morning. On delivery the child was dead and subsequent autopsy showed fractured ribs and injuries to the lung and liver. All measurements and other evidence of maturity indicated the child to be of at least 28 weeks' gestation and there was, in fact, nothing to indicate that it could not have lived. A retro-placental blood clot was demonstrated. The accused man was acquitted of the charge although neither maturity nor cause of death *in utero* was seriously challenged.

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Section of Laryngology

President—J. ANGELL JAMES, M.D., M.R.C.P., F.R.C.S.

[*May* 3, 1957]

DISCUSSION ON TUBERCULOUS CERVICAL ADENITIS

Mr. T. J. Wilmot:

Tuberculous cervical adenitis is now an uncommon condition in many parts of Great Britain, but it is still by no means uncommon in Northern Ireland where I have treated over 80 patients during the past five years.

This condition was discussed by the Section of Pædiatrics of this Society exactly a year ago (*Proceedings*, **49**, 969); many opinions expressed at that meeting will be in agreement with those put forward now.

When I was a student I was taught that one of the indications for tonsillectomy was tuberculous adenitis of the cervical lymph nodes; but I seldom saw tonsillectomy performed for this reason and I never saw the results of histological examination of tonsils removed on this account. Treatment of these cases was left largely in the hands of the general surgeons and the tonsils were often left undisturbed. An ear, nose and throat surgeon, trained in the detailed anatomy of the neck, trained to examine the throat and the pharynx with its extensions, and trained in the art of tonsillectomy, is the best fitted to deal with this condition. All my cases have been seen and treated in conjunction with Dr. Edwin James, the chest physician for this area.

Clinical Material

This paper is based on 78 patients seen between November 1951 and July 1956. The vast majority of these (73%) have shown involvement of the upper deep cervical lymph nodes, either alone or in conjunction with other lymphatic groups (Table I). In the 57 with involvement of this group of nodes, the infection has been unilateral in all but two, i.e. in 96·5%.

TABLE I.—GROUPS OF LYMPH NODES AFFECTED

Upper deep cervical	57
Submandibular	5
Supraclavicular	2
Posterior triangle	2
Submental	1
More than one group	11
Total	78

Age Incidence

Tuberculous cervical adenitis is regarded as being a disease of children and the maximum incidence occurs in childhood, but 44·8% of our patients were over the age of 15 when first seen and 34·5% were over the age of 25 (Table II).

TABLE II.—AGE INCIDENCE WHEN FIRST SEEN

	Five-year periods			Ten-year periods				
Age	0–4	5–9	10–14	15–24	25–34	35–44	45–54	55+
No. of cases	3	26	14	8	11	10	5	1

Clinical Appearances

The characteristic feature of most of these patients is the complete lack of constitutional signs. As Dr. F. J. W. Miller has pointed out (1956), these do occasionally occur in the form of a febrile reaction with early softening, but this has been a very rare phenomenon in this series. The patient usually presents with a lump in the neck which may be quite recent or may have been present for months or years (Table III).

TABLE III.—LENGTH OF TIME SWELLING PRESENT WHEN FIRST SEEN

Less than one month	8
One to three months	22
Four months to twelve months	16
Between one and three years	19
Between three and nine years	4
Ten years and over	7
Total	76

In only 4 (5·1%) did active pulmonary tuberculosis accompany the cervical adenitis. 1 patients (20·5%) gave a history of previous tuberculosis and in 2 of these the previous lesio had been a cervical adenitis. In 94·9%, however, the cervical lesion was the only evidenc of active tuberculosis during the time they were under our care.

The Role of the Tonsils

It has been part of this investigation to attempt to clarify the role played by the tonsils i this infection. Tonsillectomy has been performed in 44 patients; in 27 of these all tissu removed, including any adenoid tissue, has been examined histologically by Dr. J. Edga Morison of the Central Laboratory, Belfast. Of these, 12 (44·4%) showed evidence o tuberculosis in the tonsils and 1 case showed tuberculous infection in a small adenoi remnant. The appearances of the tonsils on clinical examination are of little or no significance and are no guide to the presence or absence of tuberculous infection. We believe tha with such a high tuberculous incidence, the tonsils should be removed in all cases where the deep cervical chain is involved unless there are strong contra-indications. Moreover, like Dr. Miller, we believe that intercurrent infection plays an important part in causing softening of previously quiescent but enlarged nodes. We think that non-specific tonsillitis is especially important in this respect and is another good reason why the tonsils and any other infected foci in the mouth, nose and throat, should be removed. Mr. Denis Browne has advocated this policy for many years but it does not appear to have been widely practised. I feel that the main clinical responsibility should be in the hands of ear, nose and throat surgeons. The general surgeon often feels that tonsillectomy is of little or no value: he does not, however, see the full clinical picture of this condition.

Management

Once active tuberculous infection of the cervical nodes is suspected, active steps should be taken to confirm the diagnosis and institute treatment. Our policy is to admit all patients to hospital within a few days. A thorough general examination is then made, an X-ray of the chest and, if necessary, of the neck carried out and tuberculin sensitivity tests done. The latter are of considerable diagnostic significance; in 50 recorded and proved cases 31 were positive in a dilution of 1/10,000, 13 in a dilution of 1/1,000 and only one was negative. Once the diagnosis has been confirmed, or is strongly suspected, chemotherapy is commenced and continues throughout surgical treatment and for a total period of not less than three months.

Where the disease is bilateral and extends well down the neck, extension from the mediastinum should be suspected. Chemotherapy, prolonged if necessary for many months, is then the treatment of choice and surgery should be limited to aspiration or curettage of cold abscesses, although limited surgical excisions may be possible at a later date. In 73 of our 78 cases (94%), however, the infection was unilateral, being localized to one or more of the upper groups. In 57 patients (73%), the upper deep cervical group only was affected and our treatment of these was basically excision if uncomplicated, or not responding rapidly to simpler measures. Calcified nodes are not excised but a partially calcified node, guilty of frequent flare-ups, is better excised in a young patient. Once surgical treatment has been completed, the patient is sent home and continues his chemotherapy under the direction of his general practitioner.

All specimens of tuberculous material have been examined bacteriologically by Dr. Violet Reilly who was able to demonstrate tubercle bacilli in 39 out of 51 patients but has only been able to culture these organisms on four occasions. Of these, three have been human and one bovine. This is in agreement with her general finding, published in 1950, that extrapulmonary tuberculosis in Northern Ireland is commonly human in origin.

Surgical Principles and Technique

Surgery is directed first towards the glands if there is softening or frank abscess formation because delay makes excision more difficult and is likely to lead to greater skin involvement with consequent scarring. If no evidence of softening is present, surgery is directed first towards the tonsils and adenoid tissue or towards eliminating dental sepsis. Whether any of these structures is infected with tubercle bacilli or pyogenic cocci is immaterial, infection is better eliminated. These simple procedures alone will be sufficient to allow many glands, at first thought to be tuberculous, to resolve without further treatment. In such cases, the tuberculin skin reactions are usually negative and the X-rays of chest normal. If the gland does not reduce rapidly in size after tonsillectomy, the patient can be sent home on chemotherapy. If the affected gland increases in size or shows any tendency to break down, excision is then performed without delay. In our series, in 40 cases where the clinical diagnosis of tuberculous adenitis was not in doubt, 33 did not resolve on chemotherapy and had a later surgical excision carried out (82·5%). There is much to be said, therefore, when everything indicates an isolated gland infection, for following up the tonsillectomy by a routine dissection of the gland. This I have done increasingly often as the series has continued.

All surgical treatment, once the diagnosis has been confirmed, has been carried out under isoniazid 5 mg. per kg. with PAS in doses of one cachet (1·5 grams) for each 50 mg. tablet of isoniazid. In very young children isoniazid syrup was given instead of tablets and the PAS was omitted. Chemotherapy has not, in our view, however, proved effective in clearing up the infection unaided and this is in keeping with the mechanical difficulty in getting the agents into the avascular tissue affected.

It is often possible to excise a cold abscess and underlying node in one mass. If the overlying skin is involved, but not extensively, it should be sacrificed: it should not be allowed to delay surgical excision, but on the contrary, should spur the surgeon on to early action. If skin involvement is extensive, preliminary aspiration or curettage with more prolonged chemotherapy may be necessary to reduce the lesion to satisfactory surgical dimensions. Here, experience is the best guide. When dissecting the skin over a cold abscess, the use of fine plastic surgery skin hooks is helpful. Careful, gentle, anatomical, sharp dissection of the whole lesion should be carried out, and suction should be available to remove any tuberculous pus. The key to most of these dissections is the sternomastoid muscle; once this has been carefully defined from the surrounding, and often dense, fibrous tissue, other landmarks become plain. Gentle retraction and the use of fine plain catgut rather than diathermy, facilitate healing which is usually very rapid. Incisions, of course, are placed in the line of the skin creases and only the minimum of skin is excised when it is inevitable. All obviously tuberculous glands should be excised, but normal glands should be left *in situ*.

When a diffuse tuberculous mass is present, prolonged chemotherapy is often successful in reducing this to a more localized lesion which can be excised. Sometimes, however, a cold abscess is so extensive, or in such a position, as to preclude excision. Under these conditions, the method I have found most successful is to open the area widely, using a skin-crease incision, and curette both abscess and the gland responsible for it under direct vision. The incision is then stitched carefully allowing room for a small drain and a polythene irrigation tube through which the cavity may be irrigated with PAS solution.

Any residual gland tissue can, if necessary, be excised later. In the few patients where I have used this method there has been no secondary infection.

All wound cavities, before suture, have been irrigated with PAS solution. In spite of the spilling of tuberculous pus and tedious, lengthy dissections, all our wounds have healed by first intention. There is little or no post-operative pain and children have the minimum of painful ward dressings. There is no doubt in the minds of most of the patients that they suffer more after tonsillectomy than after the neck dissection.

Results

Of those patients deemed suitable for surgery, 52 had an excision of glands carried out and of these, 3 developed recurrence deep to the cervical scar. These were treated by further excision and have not, to date, recurred again (Table IV).

TABLE IV.—RESULTS

Excision	52	3 Recurred. Treated by re-excision
		\+
		49
Subsided after: Tonsillectomy		7 No recurrence 1–5 years
Adenoidectomy		1
Minor surgery (aspiration, &c.)		5
Unsuitable for surgery because of long-standing, widespread, recurrent adenitis		6 Subsided with chemotherapy
Not considered for surgery because of coincident pulmonary disease		3
Subsided with chemotherapy alone, surgery not necessary		2
Refused operation		1
Died (coincident Hodgkin's disease)		1
Total		78

Simpler methods such as aspiration, incision and curettage were employed in only 11 patients; in 6 of these excision was later carried out. No skin grafts have been necessary.

Of the excised glands 49 were upper deep cervical, 8 were submandibular, 1 was submental, 1 was facial.

The results of excision have been good both clinically and cosmetically. In all but 3 of the patients operated on, the cervical lesion appears to have completely cleared up. In those whose glands recurred, a further simple excision and continuation of chemotherapy has resulted in apparent cure. We have not found it necessary to deal with these patients

as is so often advocated, by prolonged rest and other general measures; once the cervical lesion has been excised, convalescence need not be long and it has been our practice to return children to school within two or three weeks of the operation. Stay in hospital has been short following gland dissection, many patients have been home on the fifth day and the average has been between seven and eight days. Because of poor rural communications many patients have had to stay longer than was strictly necessary.

Operative Complications

(1) *Nerve injuries.*—The spinal accessory nerve was divided in one case where a large mass of glands had been present for two years and did not respond to chemotherapy. The nerve was traced into and out of the mass but could not be freed. It was divided. In this case, full function has returned to the affected muscles.

In 3 patients the cervical branch of the facial nerve has been cut; in only 1 of these is any weakness of the angle of the mouth now visible.

(2) *Keloid formation.*—Only in 2 patients has this occurred and then only to a minor degree. Both have received suitable radiation therapy with benefit.

Conclusion.—I believe that the E.N.T. surgeon is, or should be, the surgeon best equipped to deal with tuberculous cervical adenitis—a problem which is so closely integrated with oral and pharyngeal sepsis. Co-operation with the chest physician for the area is, however, highly desirable.

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Mr. J. J. Mason Brown:

Incidence of the Disease

Admissions to the general surgical wards of a children's hospital give some indication of the incidence of cervical glandular tuberculosis.

In 1924 to 1925, 221 children were admitted with this diagnosis (110 patients per year). At this time also large numbers of children with cold abscesses were treated as out-patients but there is no means now of assessing their numbers. In the period 1947 to 1951 there were 78 admissions (16 per year) and from 1952 to 1956 there were only 43 admissions (9 per year). In the past ten years outpatient treatment has not been practised so that there has been a marked fall in the numbers coming for surgical treatment and probably also in the incidence of the disease.

The age incidence for 121 patients below the age of 12 is shown in Table I. The numbers

TABLE I.—TUBERCULOUS CERVICAL ADENITIS 1947–1956

Age Incidence

Year of life	Patients
1st	1
2nd	6
3rd	4
4th	11
5th	7
6th	10
7th	12
8th	13
9th	16
10th	16
11th	17
12th	8
All under 12	121

are too small to draw definite conclusions but the maximum incidence appears to be from the 7th to the 11th year although it is found at all ages and its frequency in the second year of life is not always appreciated. Of the 121 patients 58 were boys and 63 girls so that the sex incidence is practically equal.

Incidence in Town and Country

91, or 75%, came from the country and only 25% from the town. This is of interest because tuberculous cervical adenitis is still a common condition in the regions with a preponderance of rural population (Davidson, 1957). During the same period there were 18 children with other than cervical peripheral glandular tuberculosis and 13 of them, i.e.

72%, came from the towns. It seems that the country child is likely to develop cervical glandular tubercle whereas the town child is more likely to develop peripheral adenitis in other sites. The greatly improved social conditions, the rigid control of foodstuffs, the development of tuberculin-tested herds and the universal sterilization (in the towns at least) of all other grades of milk are responsible for the falling incidence of tuberculous cervical adenitis. The greater proportion of these cases results from bovine infection and it is not surprising that the greatest incidence is in country children. Indeed, there is good evidence that 2 of the children included under town cases acquired the infection as the result of a "nice country holiday". In the extra-cervical cases of peripheral glandular tuberculosis the organism gains entry through some breech in the skin surface and most of these cases have been in town children living in poor surroundings and in overcrowded conditions, and the source has been contact with a case of tuberculosis either directly or indirectly.

Pathology

Rational treatment must be founded on an understanding of the pathology. If tuberculous cervical adenitis is the glandular component of a primary tuberculous infection or complex, e.g. with the primary focus in the tonsil and spread to the jugulo-digastric glands or a primary infection in a tooth socket with spread to the submandibular nodes, bovine infection would be most likely and an attempt to remove the primary focus and the glandular component of the primary complex would be justified. If, on the other hand, the disease is a secondary spread from a primary complex elsewhere surgical treatment would be of no value except in the treatment of complications. Most children with tuberculous cervical adenitis show no evidence of another primary complex and section of the tonsils confirms that they are infected so that there seems little doubt in most cases that the lesion is the glandular part of a primary complex.

The behaviour of the cervical nodes resembles closely that of the nodes in peripheral adenitis following infection at the site of injury or injection (Miller, 1953). In the neck the nodes most often affected are the tonsillar glands and the submandibular node which between them drain a large part of the mouth and pharynx which are not readily examined and in which it is difficult to demonstrate a primary lesion. The tonsils may look normal and yet be the site of tuberculous infection. Primary tuberculous infection does occur in the mouth but its true nature may not be appreciated. Boyes *et al.* (1956) report 7 cases aged from 2 to 17 years, only 1 being over the age of 10. The lesion presents as a painless ulcer which usually follows trauma, such as tooth extraction, and there is early involvement of the regional nodes. In any tuberculous adenitis there is always one node in the gland mass which overshadows the rest, it is bigger, it appears first, it is the first to show periadenitis and the first to soften and the primary focus is in its catchment area.

The Aims of Treatment

As cervical glandular tuberculosis is usually the glandular component of a primary complex the aims of treatment must be to eliminate the infection in the shortest possible time with the least possible disturbance of the child, to secure healing without scarring and to prevent dissemination of the infection. Antibiotic therapy might be expected to fulfil these aims.

The results of antibiotic therapy.—If the glands are firm and of recent origin when therapy is begun the gland mass shrinks but one main gland remains large and may flare up and soften despite long-term use of isoniazid and PAS. There is no doubt that a four-weeks' course of streptomycin and PAS will shrivel the glands and make them less matted to each other but it is not long after the cessation of treatment before the glands soften. In addition the exhibition of isoniazid may cause the rapid breakdown of tuberculous cervical nodes and so precipitate abscess formation (Lincoln, 1956). It seems, therefore, that with the antibiotics at present available we can fulfil the aims of treatment only when treatment is begun at a very early stage. When a new and potent drug becomes available the usual tendency is to expect too much from its use, e.g. penicillin in acute osteomyelitis and Eumydrin in pyloric stenosis. The indications for surgical treatment previously worked out from a wealth of clinical experience tend to be forgotten and have to be re-learned if the drug does not come up to expectations.

The Possibilities of Surgical Treatment

Having accepted that the antibiotics cannot fulfil the requirements of treatment and believing that cervical adenitis is a primary complex, what has surgery to offer in its treatment? Logically both the primary focus and the nodes should be removed as soon as possible to prevent the further spread of infection. Which should be dealt with first? Swenson and Small (1952) advise removal of the primary focus, i.e. usually the tonsil. They advise that if a child presents with unilateral, matted, non-tender, cervical nodes of six weeks' duration or more, and the tuberculin reaction is positive, the tonsils and adenoids should be removed

immediately. If after two weeks the nodes are still enlarged they are excised. This seems to be an over-simplification because subacute non-specific cervical adenitis may last for more than six weeks and may take much more than two weeks to subside following tonsillectomy and in England and Wales 45% of children aged 14 have positive tuberculin reactions (Brigg *et al.*, 1955). If the tuberculin reaction becomes positive during the course of the adenopathy there is little doubt about the diagnosis. The problem is more difficult than Swenson makes out, for patients present in very different ways. There may be gradual insidious enlargement of a node. There may be a history of recent illness or the onset may be acute with systemic upset, well-marked fever and rapid enlargement of the node which is fairly acutely tender. Abscess formation occurs rapidly even if antibiotic therapy is given. The lesion may well be confused with acute adenitis and its true nature is realized only when the bacteriological report on the pus is received.

Other cases present with features between these two extremes, while yet again in other cases the general reaction of the child appears to have dealt with the infection and the glands calcify. Many of these calcified glands are only quiescent and await their opportunity when the child's resistance is lowered to flare up and form abscesses which may discharge on the surface leaving a sinus. X-ray evidence of calcification must not be taken as proof of healing. Tuberculous adenitis is seen in the following stages: (*a*) glands enlarged, firm and discrete; (*b*) the glands are firm for the most part but the largest one shows periadenitis and may show early softening in the centre; (*c*) there is cold abscess formation without skin involvement; (*d*) there is skin involvement shown by adherence and redness; and (*e*) the case is one of some standing which has been treated unsuccessfully and there are sinuses, recurrent abscesses or abscesses in calcified nodes.

In cases similar to those described by Swenson and Small (1952) the treatment should be by the immediate administration of antibiotics and by tonsillectomy. The tonsils are submitted to thorough histological examination. The decision regarding the nodes depends on the tonsillar biopsy; if tubercle is found the glands are removed by a limited excision but if the biopsy does not show tuberculosis the nodes are kept under observation. If the main gland remains enlarged there is good reason to suspect it and the cessation of antibiotic therapy is likely to be followed by softening and abscess formation and skin involvement will occur sooner or later. It might be argued that to remove the tonsils first runs the risk of precipitating secondary infection in the nodes while removal of the nodes first opens up the tissues of the neck to the spread of infection from the primary focus. It seems logical to remove the primary focus at the earliest possible opportunity.

Limited excision of the nodes implies the removal of the main gland and those immediately related to it, and not a radical block dissection. Objections to radical excision are that it causes deformity because of the extensive removal of the subcutaneous tissues. This is certainly a valid criticism of radical excision done for late cases in which other methods have failed but is then not a criticism of the method but of the delay which rendered it necessary. The slight deformity which follows limited excision should be compared with that due to abscess formation which may be prevented by timely excision.

Results of Surgical Treatment

In this series of 121 cases (Table II) excision was carried out in 45 as the first form of

TABLE II.—SURGICAL TREATMENT 121 PATIENTS

148 *Operations*

Aspiration	7	Failure	6	(86%)
Incision and expression	10	Failure	4	(40%)
Incision and curettage	62	Failure	21	(34%)
Primary excision (no abscess)	31	Failure	1	(3%)
Primary excision (small abscess)	14	Failure	2	(14%)
Secondary excision, i.e. after failure of other methods	24	Failure	0	
All excisions	69	Failure	3	(4%)

surgical treatment (other than tonsillectomy) they received. In 31 there was no clinical evidence of spread beyond the nodes and there was one failure, i.e. further treatment was required. In 14 children there was evidence of softening and periadenitis but no evidence of involvement of the skin and there were 2 failures. Excision was used also as a secondary treatment when all other methods had failed and when abscess formation arose late in the apparently quiescent case with calcified nodes. Such secondary excision was done in 24 patients and was successful in all. In all, therefore, excision was carried out on 69 occasions and only 3 required further surgical treatment.

In 121 children there were 148 operative procedures including aspirations, but excluding procedures carried out at other hospitals. The 69 excisions have been considered already.

The remaining 79 operations (Table II) were, incision and curettage 62 with failure in one-third of cases; incision and expression 10 with 40% failure; and aspiration 7 with success in only 1 case.

It is a fundamental mistake in treatment to allow abscess formation to occur except in cases which present acutely when it cannot be avoided. Limited excision under antibiotic cover at an early stage is a most valuable method of avoiding abscess formation and its complications and of cutting short the otherwise long period of treatment. The prolonged period of antibiotic treatment of this glandular part of a primary complex is not justified at this age although it would be if it could eradicate the disease or prevent its recurrence. In the present state of our knowledge and with the antibiotics at present available surgery is indicated (*a*) to remove the primary focus be it tonsil or tooth, (*b*) to remove the nodes if the tonsils are tuberculous and if they do not subside, (*c*) for the treatment of complications arising during and following the stopping of antibiotic therapy, and (*d*) for late abscess and sinus formation in previously treated cases. Lastly, the unsightly adherent scars following incision and curettage, aspiration or incision and expression may be greatly improved by surgical means when it is certain that the disease is quiescent.

These are not many cases on which to base conclusions but I recall the very large numbers of children treated surgically so effectively by my predecessors Miss G. Herzfeld, Sir John Fraser and Sir Harold Stiles, without the aid of antibiotics. Surgery should not be abandoned or relegated to the treatment of cold abscesses. At present the optimum form of treatment is a combination of antibiotics and surgery. The surgeon should have the opportunity of assessing the patient before there is skin involvement. The place of surgery is not solely to retrieve the failures resulting from other methods of treatment.

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Dr. E. F. James:

My particular concern is the diagnosis and treatment of chest diseases, but the most prominent of these is tuberculosis, and as there are certain basic similarities between tuberculous lesions wherever they occur in the body, it is not possible to deal with pulmonary tuberculosis without being interested in the disease as a whole. I have concentrated, therefore, on the more general implications of this study of cervical adenitis, in the hope of gaining information about the mysterious behaviour of tuberculosis.

The infectiousness of tuberculosis cannot be doubted, yet out of 78 cases of cervical adenitis an obvious source of infection was found in only one, although 164 family contacts were X-rayed. We believe that the human tubercle bacillus was responsible for the majority of our cases, and a family history of pulmonary tuberculosis was found in 10 cases, but, apart from the one mentioned above, the history was remote and no active disease was present in the family at the time the cervical adenitis presented itself. If it had not been for our previous knowledge of the tubercle bacillus, therefore, there was little to suggest that we were dealing with an infectious disease.

The first outstanding feature of our patients was that the lesions almost always were sharply localized; only 4 patients had active tuberculous lesions elsewhere. It is true, of course, that tuberculosis can be generalized in the shape of miliary disease and meningitis, but these are now rare and have always been relatively uncommon. It is also true that a patient can have multiple tuberculous lesions, but in my experience it is most unusual to see more than one active lesion in a person at the same time.

The second outstanding feature was the absence of constitutional symptoms. An excellent general condition was the rule, and we found no clinical evidence to suggest a lowering of general resistance to tuberculosis, of which the adenitis was a local manifestation. Consequently when the local lesion was efficiently treated, recovery was rapid and complete. Rest and treatment to improve the general condition were quite unnecessary. The revolutionary benefits which have followed the discovery of specific anti-tuberculous drugs have focused attention on the importance of treating the tuberculous lesion, and a logical outcome has been the widespread use of surgery in dealing with obstinate lesions. The new drugs when they do not offer definitive treatment, and they rarely provide it in cervical adenitis, at

least permit the surgeon to operate without the risk of precipitating generalized tuberculosis. Although in theory tuberculosis is a general disease, in practice it is astonishingly localized, and the application of specific anti-tuberculous treatment has shown that if we treat the lesion, the patient can be left to take care of himself. Our study of these patients gave us a picture of a disease in which evidence of recent infection was difficult to find. Indeed, in one case there was an interval of forty-two years between what we took to be the time of infection and the appearance of the adenitis. We formed the impression of tuberculous infection rather as something which sets the stage for later events than as a cause of immediate disease. This does not diminish the importance of infection, indeed it increases it, because it means that anyone who has been infected with tubercle bacilli, however little disturbance they have caused on entering his body, is liable to develop a destructive tuberculous lesion, if suitable conditions arise.

What are these suitable conditions? It seemed to us that the disease arose because of a local and not a general breakdown in resistance, and here it might be helpful to remember the phenomenon of tuberculin hypersensitivity. When a person is infected for the first time with tubercle bacilli, his tissues become hypersensitive to the protein portion of the bacillus, broadly described as tuberculin. After that, a test dose of tuberculin injected into the skin will produce a reaction, varying according to the dose and the degree of hypersensitivity, from inflammation to necrosis and sloughing. The same inflammatory effect may be produced on any dormant tuberculous lesion which the person may be harbouring and tuberculin can change an inert caseous mass into an active tuberculous abscess. The result of injecting tuberculin, therefore, can be the same as that which follows the multiplication of tubercle bacilli in a lesion, or a fresh infection.

We believe that non-specific pyogenic or virus infection can behave like an injection of tuberculin in activating old tuberculous foci and that this mechanism is often responsible for determining the onset of tuberculous cervical adenitis. Jones (1951), in an excellent paper on tuberculous lymphadenitis in the Nigerian African, stated quite positively that non-specific pyogenic infection of the tonsils and teeth was the important ætiological factor in cervical adenitis in the African, because of its sensitizing effect on pre-existing tuberculous foci. The evidence incriminating non-specific infection is circumstantial as far as the glands are concerned but I have seen some cases which would seem to demonstrate its operation in the lungs. It seems reasonable, therefore, to offer the conception of the origin of tuberculous lesions at the site of old infection from the action of an excess of hypersensitivity, generated by accidental extraneous factors.

It would be dogmatic to suggest that all lesions arise in this way, and progressive tuberculosis following immediately on primary infection is well known. Nevertheless, I believe that this theory accounts for the majority of cases of tuberculosis. If it is accepted it becomes obvious why the link between infection and disease is so difficult to establish, and why a tuberculous lesion can suddenly arise in a person who appears to be in perfect health. It would also explain why the modern treatment, which is directed mainly against the lesion, is so strikingly effective and why, although tuberculosis mortality is now negligible in the United Kingdom, morbidity is falling much more slowly. The most rational approach to tuberculosis would seem to be to seek it diligently and to treat it vigorously until eventually there is an uninfected community in which tuberculous disease is unknown.

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BOOK REVIEWS

The Voice and Its Disorders. By Margaret C. L. Greene, L.C.S.T. (Pp. ix + 224; illustrated. 45s.) London: Pitman Medical Publishing Co. 1957.

This book of 224 pages contains a considerable amount of useful information. It describes first the normal mechanisms of voice production and this takes about a quarter of the book. The rest of the book is devoted to disorders of the voice and the methods of correction. Illustrative case histories are given in this section and they are of considerable help in demonstrating the scope of speech therapy. It is important that a speech therapist should know something of the pathology of the voice disorders that are referred for treatment, but this limit has been exceeded in this book and the medical sections have become a rather bad and inaccurate textbook of laryngology. It is in this way that this book goes wrong even if the facts were right. For example, much unnecessary information is given, the diagnosis of syphilis, the symptoms of hyperthyroidism, clinical details of cancer, the place of irradiation in the treatment of cancer, the use of drainage after laryngectomy and many other slightly misleading snippets of clinical information. Surely a textbook on speech therapy is no place to discuss the relative merits of and indications for the various possible treatments of cancer of the throat, as is done on page 185.

The physiology of respiration is described in a manner which suggests a scientific accuracy which is not present. If the breath is held till the subject swoons he will become unconscious because of cerebral anoxia and not carbon dioxide poisoning as stated on page 14. Furthermore forced respiration of air, 20% oxygen, will not cause swooning from excess of oxygen. After forced respiration the respiratory centre does not "comfortably take charge of the situation". There is a period of apnœa due to carbon dioxide tension having been reduced by the forced respiration and it is some time before normal respiration is re-established.

When the author discusses speech therapy she is on much surer ground and she writes with authority. She realizes that the main function of the speech therapist is to encourage the patient, to improve his morale and to show him how to improve his voice. She emphasizes the need for auditory training so that the patient can hear his own faults and she points out the value of recording the patient's voice and playing it back to him and thus demonstrating his faults and also demonstrating improvement as the therapy progresses. Her methods of teaching œsophageal speech are good and once again she realizes that the therapist gives encouragement and one of her main functions is to arrange for other laryngectomized patients with good speech to see the patient and show him what can be done.

There is an extensive bibliography at the end of the book, but the quotations from these papers are not always digested before being quoted. For example these contradictory statements occur on consecutive pages: Unilateral abductor paralysis. This is the most common of the post-thyroidectomy complications. Complete unilateral recurrent paralysis. This is the most common type of paralysis and accounts for 90% of all vocal cord palsies. Functional aphonia following thyroidectomy. It must be stressed that by far the most common voice disorder following thyroidectomy is an hysterical one.

It is interesting to speculate on the conclusion a student would reach after reading and comparing these three statements.

The impression given by reading this book is that the author knows speech therapy and teaches it well. The sections dealing with speech therapy are clear and authoritative and easy to read. There are, however, errors and half-truths in the physiology and pathology and discussions on the choice of surgical treatment are out of place in a book like this. If these sections are to be included in a book of this sort there should have been closer collaboration with laryngologists so that the obvious errors could have been excluded. In the opinion of the reviewer the scope of this book is too great to have been undertaken by a speech therapist without a medical co-author.

Gastro-duodenal Ulcer. Physio-pathology, Pathogenesis and Treatment. By J.-Jacques Spira. (Pp. xvi+549; illustrated. 73s. 6d.) London: Butterworth & Co. (Publishers) Ltd. 1956.

The author of this handsomely produced book has spent much of his professional life in studying the problems of the ætiology of peptic ulceration and of its management. He has read widely on the subject whilst developing his theses, and has collected a bibliography which is so large that it occupies over 150 of the total of some 550 pages that make up the book. This is possibly the most valuable part of this book, but its usefulness might have been greater if the bibliography had been broken up and classified so that the relevant references came at the end of the individual chapters and sections.

The book begins with a review of the physiological and pathological considerations, and

leads on to a discussion of the ætiology of gastro-duodenal ulceration and the elaboration of the author's own theories on the subject.

These centre round his belief that fats are of major importance in the production of peptic ulceration. It may not be felt that this adds anything of fundamental importance to the elucidation of the subject or that his method of treatment is particularly revolutionary. There will, however, be none who will deny the truth of the widely appreciated advice to avoid stooping after a meal and the unwisdom of taking articles of food which are known to lead to discomfort.

An Introduction to Electrocardiography. By L. Schamroth, M.B., B.Ch.Rand., M.R.C.P.E., F.R.F.P.S. (Pp. xi + 60; illustrated. 12s. 6d.) Oxford: Blackwell Scientific Publications. 1957.

There is no dearth of textbooks on electrocardiography, but many of them deal with the subject at such length as prove cumbersome to the physician who needs a convenient guide to the interpretation of occasional tracings. This small manual is meant to supply this need. In many places, however, a description of the clinical state is introduced, but its brevity makes it unhelpful. Moreover, the bipolar chest leads (CR) receive no mention in spite of their undoubted superiority over Wilson's so-called unipolar leads, in the diagnosis of cardiac pain.

No natural electrocardiograms are shown, and the tracings are portrayed as line drawings, admittedly well executed in many respects, but giving them an artificial appearance, and a false impression of the design of the QRS complex, and particularly of the S–T segment.

The purpose which this manual best fulfils, and fulfils well, is the graphic illustration of the basic principles of electrocardiography. As an introduction to the subject it is well worth possessing, and the absence of natural electrocardiograms has allowed its publication at a low cost.

The Principles and Art of Plastic Surgery. 2 Vols. By Sir Harold Gillies, C.B.E., F.R.C.S., and D. Ralph Millard, Jr., M.D. (Pp. xxi + 652; illustrated. £12 10s.) London: Butterworth & Co. (Publishers) Ltd. 1957.

It was expected that a book by Sir Harold would be an exceptional one. His unrivalled experience in plastic surgery, and his unorthodox and provocative approach demand attention, while his co-option of a younger co-author at least promised that the narrative would be readable.

Simple handling of the volumes shows that they are impressive, and the publishers are to be congratulated on a very fine production. The number of illustrations is prodigious, and this alone must have given great difficulty in production. The provision of photos and drawings at the side of the text on nearly every page is something that publishers shrink from, and Messrs. Butterworth have set a standard that it is hoped will be followed. The reader will appreciate the pleasure of finding the text and appropriate illustrations on the same page.

As to the style and composition, it is clear that this work is not a textbook comparable to any other. It is a history of the development and progress of plastic surgery, closely woven with an autobiography and biography of the senior author and his colleagues.

The chapter of acknowledgments is graceful, but suffers from too many superlatives. All Sir Harold's geese have got to be swans! The use of slang and of colloquial terms is frequent throughout the book, and will be irritating to many who may find them as puzzling as the sudden appearance of P.A.W.G. (postauricular Wolfe Graft)! On the other hand, these terms and the humorous reminiscences that go with them will bring pleasure to those who have been associated with Sir Harold.

A commentary on each chapter is impossible, but as one reads one realizes that the story of plastic surgery and that of Sir Harold are one and the same. His restless energy and enthusiasm, his ingenuity in meeting surgical problems, are all portrayed, and noteworthy is his ability to apply the techniques of others to solve his own puzzles. The use of Esser's inlay for the correction of ectropion is an example of his questing brain, and the use of the epithelial inlay behind the syphilitic nose was brilliant in conception. The recognition of the first tubed flap in 1917, and the implications and application were probably realized in a flash, and formed the basis of all tubed flap work ever since. At the same time, Sir Harold has had the provocative faculty of stirring his colleagues from self-satisfaction into a state of indignant thought.

Every chapter shows how the early problems were met and treated, and the same problems are therefore the easier to manage to-day—inlay grafting, flaps, cross leg flaps, lymphœdema. Some of the results are astounding, and one wonders how some of the large scale flaps ever survived.

This is a magnificent publication, full of humour and helpful advice on all the plastic problems.

Section of Epidemiology and Preventive Medicine

President—IAN TAYLOR, M.D., M.R.C.P., D.P.H.

[*May* 31, 1957]

DISCUSSION ON POLIOMYELITIS VACCINATION IN 1956

Professor C. H. Stuart-Harris (Department of Medicine, University of Sheffield):

Our story begins in 1955 when the first supplies of poliomyelitis virus vaccine became available in this country. The vaccine, made according to the original formula as described by Salk (Salk *et al.*, 1953) had been prepared by Dr. W. Wood of Glaxo Laboratories. The original M.R.C. Working Party on polio planned to use this first limited supply by inoculating it into groups of adults and then into children. Antibodies to the three polio viruses were to be measured before and after inoculation and the serological response was to have been compared with results obtained in experimental animals. Beyond these serological trials no one could tell where the story might lead when, in April 1955, the report of the Vaccine Evaluation Centre of the University of Michigan was released (Francis *et al.*, 1955). This American trial, which was probably the most careful large-scale study of any prophylactic ever undertaken, appeared to establish the effectiveness of 3 doses of the Salk vaccine in school-age children. The impact of this report, which was released with an unprecedented display of publicity, had hardly died away when we learnt of the occurrence of cases of poliomyelitis in groups of American children inoculated with vaccine in 1955. As the full story of what will always be known as the Cutter disaster became known (Langmuir *et al.*, 1956) it was obvious that our own plans would have to be abandoned until the cause of the setback had been ascertained. In the meantime a group of 15 adults had in fact received Dr. Wood's first vaccine and measurement of the antibody response in this group showed that the vaccine was fully antigenic (Tyrrell *et al.*, 1956).

By the autumn of 1955 it became clear that the trouble with the Cutter vaccine was due to residual live virus in the vaccine as issued. Although all three types of virus had in fact been recovered from the final vaccine, almost all the cases of poliomyelitis resulting from its use were found to have been infected by type I virus. Use of the Mahoney strain of type I virus which had been and still is incorporated in all American-made vaccine had already been criticized on the grounds of its high virulence, and it was decided that this virus should not be used in any vaccine made in Britain. While our manufacturers were seeking an alternative type I virus with a lesser power of inducing paralysis in monkeys, the Medical Research Council appointed three committees to deal with the several problems concerned in the further exploration of the use of polio vaccine. The most important of these is undoubtedly that headed by Sir Sam Bedson which, under the title of the Safety Tests Committee, has had under constant review all matters connected with the preparation of vaccine and its test under the Therapeutic Substances Act by the Biological Standards Division of the Laboratories at the National Institute for Medical Research. We shall hear something of the work of this division from Dr. Tobin who will also deal with the tests of the antigenicity of the vaccine in children. The second committee whose chairman is Professor E. T. C. Spooner was appointed to deal with all matters connected with laboratory investigations which might be required in any further studies on the vaccine. The third committee, on whose behalf I am speaking, was appointed to make observations on the clinical effects of poliomyelitis vaccine which might guide the Medical Research Council in any advice which it was required to give to other authorities.

Nothing further could be done in Britain until it was known that an alternative type I strain which was less virulent than the Mahoney virus but yet was also antigenic in animals, had been found. Fortunately Danish work (von Magnus *et al.*, 1955) with the strain of Brunhilde virus as modified by Enders in tissue culture gave us a hint and this same strain, now known as Brunenders virus, became the basis of vaccine production by Dr. Wood. When it became reasonably clear that some vaccine made from the new strain would become available in the spring of 1956, discussions began concerning its use. I shall not deal with all the arguments which occurred but merely with the conclusions. As the British vaccine contained a different strain of type I virus from that used in the Francis trial in the U.S.A., it was felt that we could not assume, without trial, that our own material would give results

comparable with the Salk vaccine. Secondly, the American vaccine left the problem of the pre-school-age child unanswered. Actually the youngest children in the American trial, who were aged 6, appeared to have received less protection from the vaccine than those aged 8 or 9. As the attack-rate and hence susceptibility of the pre-school child are higher than those of school children, it seemed to us that the vaccine ought to be tested in young as well as in older children. These two arguments led us to recommend to the Medical Research Council that a field trial of the British vaccine should be undertaken before the latter came into general use. I shall leave the further story of what ultimately transpired to Dr. Knowelden, who is the secretary of our committee and a member of the Statistical Research Unit of the Medical Research Council.

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Dr. W. Wood:

The Production of Poliomyelitis Vaccine in 1956[1]

The poliomyelitis vaccine production unit at Glaxo Laboratories was created in the summer of 1954. At this time the United States field trial of the vaccine developed by Dr. Jonas E. Salk was in progress but several months were to elapse before any assessment of its clinical efficacy was possible. At this stage then, in the latter months of 1954, work was begun at Sefton Park in Buckinghamshire on the propagation of virus strains Mahoney, MEF–1, and Saukett which were, and still are, those representative of the three antigenic types of poliomyelitis virus used for vaccine manufacture in the United States.

By the spring of 1955, three small batches of vaccine had been prepared and tested. Although it was not possible to carry through the field trial as proposed by the M.R.C., one of the batches was used to immunize a small number of staff and students at Sheffield University and the results published by Tyrrell (1956) were the first demonstration that batches of satisfactory potency were being prepared in this country.

It was at this stage that a very significant step was taken by the Medical Research Council in recommending that vaccine manufactured in the United Kingdom should be prepared from a less virulent strain than Mahoney as the type 1 component. For it had become clear during the summer of 1955 that incompletely inactivated Mahoney virus in certain vaccine batches in the U.S.A. had induced some cases of paralytic poliomyelitis. During the ensuing months many dozens of type 1 strains from both sides of the Atlantic were tested in monkeys for virulence and antigenicity. Eventually both the Wellcome Research Laboratories and ourselves, in collaboration with the M.R.C., selected a partially attenuated line of the Brunhilde strain which we called "Brunden" as the most suitable strain. This strain had been modified originally by Enders by repeated tissue culture passage in human embryonic tissue and subsequently fed to chimpanzees by Sabin, and is probably very similar to the strain which Gear (1956) has called "Brunenders". Following intramuscular inoculation in rhesus monkeys, Brunden virus produced significantly less paralysis than did Mahoney and the antigenicity of inactivated preparations of both viruses appeared comparable. Strain Brunden was therefore used as the type 1 component in the preparation of all subsequent vaccine batches. The methods employed at the main stages of the production process are outlined in Fig. 1.

Virus production.—One of the facts emerging from the U.S.A. field trial was the necessity to prepare virus fluids with at least one million infectious particles per millilitre in order to have the inactivated virus provide an adequate antigenic stimulus. Two main methods of "bulk" propagation of virus have been evolved which yield fluids of requisite titre. The most widely adopted method is an elaboration of the Dulbecco and Youngner techniques by which monkey kidney tissue is treated with trypsin and the cell aggregates so produced are grown out in stationary cultures to give a sheet of new epithelium, for the most part one cell thick. For bulk production, it is usual to use 5-litre bottles and, after a confluent monolayer of new epithelium has developed, the spent nutrient is removed and fresh medium is added

[1] *Scientific Staff engaged on Vaccine Production Project:* Mr. L. W. J. Bishop, Mr. J. C. Burge, Mr. G. J. Christofinis, Miss D. Cross, Miss J. O. R. Day, Mr. S. A. Keeble, Mr. D. E. Miller, Mrs. M. K. Smith, and Mr. F. W. Wood.

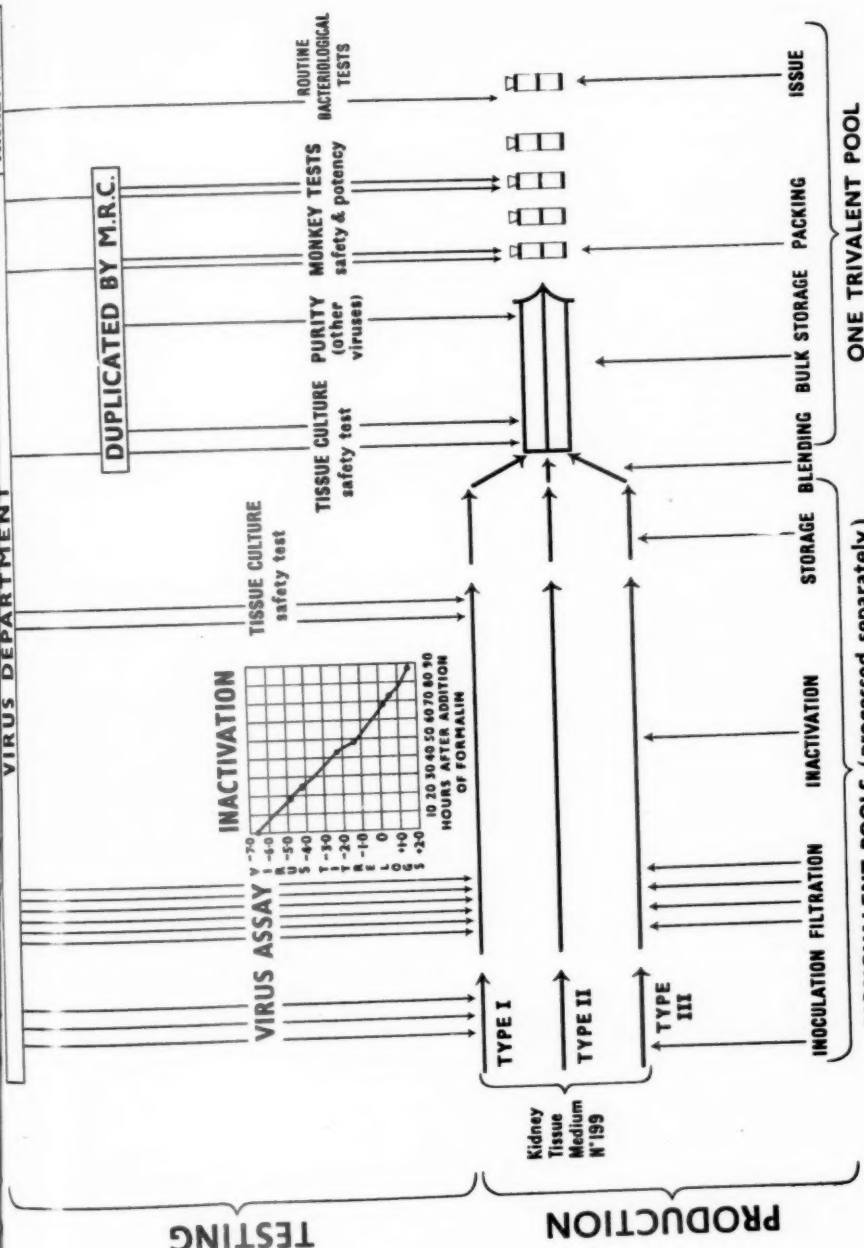

PRODUCTION OF POLIOMYELITIS VACCINE
TESTING
PRODUCTION
VIRUS DEPARTMENT
ANIMAL HOUSE
DUPLICATED BY M.R.C.
VIRUS ASSAY
INACTIVATION
HOURS AFTER ADDITION OF FORMALIN
TISSUE CULTURE safety test
TISSUE CULTURE safety test
PURITY (other viruses)
MONKEY TESTS safety & potency
ROUTINE BACTERIOLOGICAL TESTS
TYPE I
TYPE II
TYPE III
Kidney Tissue Medium N°199
INOCULATION FILTRATION
INACTIVATION
STORAGE
BLENDING
BULK STORAGE
PACKING
ISSUE
MONOVALENT POOLS (processed separately)
ONE TRIVALENT POOL

FIG. 1

together with the virus inoculum. In a few days the virus has invaded and destroyed the kidney cells and the virus progeny is released into the fluid phase of the culture which is then "harvested".

The other method of bulk preparation of poliomyelitis viruses is the one introduced by the Connaught Laboratories in 1952 and is essentially a large-scale version of the Maitland technique whereby the tissue is chopped into pieces about 1 to 2 mm. in diameter which are allowed to float free in the nutrient medium. This method was the one employed for the preparation of the virus in 1953 which was later processed into vaccine in the U.S.A. for the Field Trial in 1954 (Farrell *et al.*, 1955) and is the one we employ at Sefton Park. Superficially, it is a much less elegant technique than the trypsinized cell method and the titres of the virus pools produced are slightly lower. However, in practice, it is a most trouble-free operation to manage, and as the procedures carried out are independent of any demonstration of cell growth—which indeed may not occur—considerable latitude is available in the timing of the inoculation and harvest stages.

Virus inactivation.—Salk's method of inactivation using a 1 :4,000 formalin concentration at a temperature of 37° C. is employed (Salk, 1953). Each type of virus is inactivated independently in lots of 50 or 100 litres. The two significant changes which were introduced in the United States in the light of the early 1955 experiences, viz. the necessity to test large samples for active virus not only at the end of the inactivation period but also three days earlier; and the requirement that filtration should be carried out after formalin addition in order to break down aggregates of virus, are perhaps in themselves largely responsible for the impressive record of safety built up in the United States over the last two years.

However, in addition to compliance with formal regulations, the attention paid to the simple mechanics of the operation itself and the general lay-out of the working areas is also important. For example, the basic assumption—implicit in the performance of the required tests of safety—that the sample tested is truly representative of the bulk fluid, has involved the adoption of lengthy and repeated periods of mixing, and the frequent transfer of the bulk fluid to freshly sterilized containers. The final "trivalent" vaccine is prepared by blending one or more single strain pools of each type in roughly equivalent proportions.

Safety testing.—The principles and practice of the various safety tests which are required will be dealt with in detail in the paper by Dr. Tobin. It is noteworthy, however, that the performance of these tests on the scale required, is associated in our experience with one pressing problem which often results in delays occurring in the completion of a particular test. This is the frequency with which the kidney tissue of apparently healthy monkeys is minimally contaminated with a member of a large group of viruses, loosely designated simian or "wild" viruses (Hull *et al.*, 1957). The emergence of these viruses, sometimes after prolonged cultivation in safety test bottles requires much additional work in order definitely to associate the virus with a particular lot of monkey tissue rather than with the vaccine sample being tested.

Potency testing.—For the 1956 programme it was not possible to test for antigenic potency the individual single strain pools which were to be combined together to form the trivalent vaccine. These tests, which were performed in monkeys, were carried out only on the final triple preparation but now, to avoid the possibility of using poorly antigenic monovalent pools, potency tests are carried out at the monovalent as well as the trivalent stage.

In conclusion, I would like to record the appreciation felt by those concerned with the manufacture of this particular vaccine for the practice of duplicate safety testing of vaccine batches adopted for an initial period by the M.R.C. Control Laboratories, thus providing an assurance of safety that cannot always be guaranteed within the confines of a single testing unit.

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Dr. J. O'H. Tobin (Biological Standards Control Laboratory, Medical Research Council Laboratories, Hampstead):

Safety and Potency Testing of Poliomyelitis Vaccine

The regulations governing poliomyelitis vaccine production and testing have been laid down in a general way in the Therapeutic Substances Amendment Regulations (1956) and are based on those used in the United States. Dr. Wood has already described how vaccine is made; it is my task to describe how it is tested in the Biological Standards Control

Laboratory. After the manufacturers have tested inactivated single strain pools of each virus type for safety by cell culture methods, and for antigenicity, pools of each type are blended to form the final vaccine. 3½ litres of this, neutralized with sodium metabisulphite—but before the addition of preservatives—are sent to us for cell culture tests. 100 ml. from each filling lot, after distribution into final containers, are also sent to us for inoculation into monkeys and for potency tests. This sample is the same as that which will be used for immunization in the field. The tests we do are similar to those done by the manufacturers on the final vaccine and, at the moment, are done concurrently with them.

Vaccine testing can be divided up into three parts: (*a*) cell culture safety tests; (*b*) monkey safety tests; and (*c*) potency tests.

(*a*) *Cell culture safety tests.*—Usually 2,000 ml. of vaccine are inoculated on to monkey kidney cell cultures in Pyrex feeding bottles. These are prepared in the usual way, the cultures being grown in Parker 199 solution containing 5% horse serum free from polio virus inhibitors. After rinsing the cultures with Hanks solution, neat vaccine, freshly dialysed against Hanks and 199 solution, is added and incubated at 37° C. After three to four days, 10 ml. of 199 medium is also added to the cultures to keep the cells in good condition during the remainder of the first week of incubation. The bottles are examined twice weekly for three weeks. The culture medium is changed and samples for subculture taken after seven, fourteen and twenty-one days. These subcultures are inoculated in pools of 3 or 4 on to other bottles, which are observed for a fortnight. At the end of twenty-one days the original cultures are divided into groups and challenged with a minimal amount of stock strains of the three types of polio virus to confirm their sensitivity to these agents. We have preferred to add only 10 ml. of dialysed vaccine at first as in three experiments we have found that we get more virus "takes" with a thin layer of fluid over the cell sheet than with deeper ones.

The only real trouble we have had with our cultures is "foamy agent" (Rustigian *et al.*, 1955). This seems to be seasonal, occurring mostly in the early and late months of the year. During this time we have always tested 2½ litres of vaccine to compensate for the loss of cell sheets during the third week of incubation.

(*b*) *The monkey safety test.*—Owing to the substitution in the British vaccine of the Mahoney strain of type I polio virus by Brunenders, some modification of those methods used in the United States has been made. Brunenders (Gear, 1956) is an attenuated variant of the Brunhilde strain, isolated by Enders and further studied by Sabin (1955). As attenuated strains have been shown to be more easily isolated in cynomolgus than in rhesus monkeys, fifteen of each species are used in the monkey test. They are treated concurrently with cortisone as this drug increases the sensitivity of monkeys to the Brunenders strain and as it was in cortisone-treated monkeys that live virus was regularly isolated from American vaccine suspected of containing live virus (Eklund *et al.*, 1956; Syverton *et al.*, 1956).

The following schedule is used for the monkey test at present: 125 mg. cortisone is given two days before, and on the day of, injection of vaccine, and at least 50 mg. every other day for the following twenty-two to twenty-six days. Both rhesus and cynomolgus monkeys are injected intracerebrally, intraspinally and intramuscularly as it is thought that this is better than using any one of these routes separately (U.S. Report, 1956). Both species are observed for twenty-four to twenty-eight days and then sacrificed for histological examination of the brains and spinal cords. In addition, the cynomolgus monkeys have blood taken twice weekly for virus isolation as viræmia is a feature of polio virus infection in these animals.

We use rhesus, and not exclusively cynomolgus monkeys, as three viruses and not only type I, are used in vaccine production. MEF-1, the type II strain, is as virulent in rhesus as in cynomolgus monkeys and both species appear to be similar in their sensitivity to the type III strain.

(*c*) *Potency tests.*—Twelve rhesus monkeys are given 1 ml. of vaccine at weekly intervals and bled seven days after the third dose. The sera are titrated at doubling dilutions against 50–100 $TCID_{50}$, using two tubes per dilution. The virus/serum mixtures are held for three hours at 37° C. before inoculating them on to cell cultures. If less time of contact or a lower temperature is used, results become more irregular. We have compared the three Glaxo vaccines used last year with a vaccine kindly supplied by Eli Lilly & Co. and find they compare favourably with the American one, which we use at the moment as our unofficial standard. These vaccines have also been compared with each other using guinea-pigs and cotton rats (Perkins, 1957).

The antigenic response in children to the three batches of Glaxo vaccine has also been determined in co-operation with the Medical Research Council committee on the laboratory investigations of poliomyelitis, and is quite satisfactory (Medical Research Council, 1957). These vaccines were of the same potency whether tested in children, in monkeys, in guinea-pigs or in cotton rats. They were equally potent in children under and over 5 years of age.

Most of these children produced antibody, only 2 failing to produce some to all three types. However, some titres were lower than one would have liked. Whether all these children will respond to a booster dose of vaccine in one to two years' time is not yet known, but they are being followed-up to determine this point.

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Dr. J. Knowelden:

When the Minister of Health and Secretary of State for Scotland announced in January 1956 a poliomyelitis vaccination programme for children in England, Wales and Scotland born in the years 1947 to 1954, the Medical Research Council's Statistical Research Unit, acting on behalf of the Poliomyelitis Vaccines Committee, was invited to plan for an assessment of the protective effect of the vaccine that was to be issued later in the year. It was expected that the demand for vaccine would greatly exceed the supply, and in these circumstances of shortage it was planned to compare the incidence of poliomyelitis in vaccinated children with that in children whose parents had registered them for vaccination but for whom none was available. The selection of which children were to be vaccinated amongst those registered had to be made uniformly throughout the country and without bias to make such comparisons between incidence rates valid. It was decided to make this selection according to the month of birth.

From January to March 1956 the parents of just over 1,900,000 children, i.e. 30% of the available children in the age group approximately 1–9 years, registered them with local health authorities. Registration was about twice as frequent in school age children, born 1947–50, as in pre-school children, born 1951–54. On the basis of an estimated supply of vaccine sufficient to give two doses of 1 c.c. each to 200,000 children, it was announced towards the end of April that those selected for vaccination were the 95,723 registered children born in November of the years 1947–50, and the 98,687 registered children born in March and November of the years 1951–54. August was selected as a reserve month for any excess vaccine available after the requirements of these groups had been satisfied.

Vaccination was carried out by local health authorities from early May to the end of June; 178,161 children received two injections with at least three weeks' interval between them, and 32,379 received one only. From special studies undertaken in Buckinghamshire, London, Manchester and Sheffield it appeared that local reactions to these injections were mild. No albuminuria, or obvious excess of cells or casts was detected in an examination of specimens of urine from a small sample of children subsequent to vaccination. In the whole country illnesses possibly related to vaccination were reported in 6 children; although none was believed to be caused by the injections, the absence of comparable information from unvaccinated children makes it impossible to determine whether there was an excess of such illness in vaccinated children. 3 children developed paralytic poliomyelitis within thirty days of an injection, but none developed paralysis in the inoculated limb. 3 children developed aseptic meningitis without isolation of polio virus within the same period.

From early May 1956 local health authorities supplied case reports to the Statistical Research Unit for every notification of poliomyelitis in a child under 10 years of age. Of these reports, 512 related to registered children, vaccinated or unvaccinated. Clinical reports on these children were requested from the hospital clinicians or general practitioners, while specimens of blood and stools were examined in the University laboratories at Aberdeen, Edinburgh, Glasgow and Manchester and by the Public Health Laboratory Service. From these data the cases were classified by clinical and laboratory findings. 10 "abortive" cases were excluded as they exhibited no signs of central nervous system involvement, while 37 were not poliomyelitis at all in the clinicians' opinion.

The protective effect of the vaccine was estimated by a comparison of the incidence of poliomyelitis in vaccinated children from July 1, 1956, to January 31, 1957, with that in registered, unvaccinated, children during the same period. Prior to July 1, vaccination was still in progress and the populations at risk were unknown. All children born in August, the reserve month, were excluded from the comparison as the method of selection by which 20% of them were vaccinated was left to the individual choice of the Medical Officers of

Health and it is impossible to say what factors determined this choice in the 200 separate authorities. For various reasons 33,064 children born in March or November and eligible for vaccination received no injections. Among these defaulters those born in November 1951–54, had a higher attack rate of paralytic poliomyelitis than unvaccinated children born in other months and not eligible for vaccination. It was considered that this excess, limited to the one age group, was not evidence of a bias in those defaulting, i.e. that the vaccinated children were an unbiased sample of registered children born in March and November.

In the 74,660 vaccinated children born in 1947–50 who received two injections of vaccine, one case of paralytic poliomyelitis occurred, giving an attack rate of 1·3 per 100,000. This was only 16% of the attack rate in the corresponding unvaccinated children, 8·2 per 100,000 (Table I). 3 cases of paralytic poliomyelitis occurred in the 74,024 children born in 1951–54

TABLE I.—ATTACK RATES OF POLIOMYELITIS IN VACCINATED AND UNVACCINATED CHILDREN

	No. of children	Paralytic		Non-paralytic with virus isolation	
		Cases	Rate per 100,000	Cases	Rate per 100,000
		1947–50 *Births*			
Vaccinated	74,660	1	1·3	1	1·3
Not vaccinated ..	1,116,359	91	8·2	25	2·2
		1951–54 *Births*			
Vaccinated	74,024	3	4·1	0	—
Not vaccinated ..	446,857	90	20·1	15	3·4

who received two injections, giving a rate of 4·1 per 100,000, only 20% of the attack rate in the corresponding unvaccinated children, 20·1 per 100,000. There was a significant reduction in incidence in vaccinated children but the rates were based on too small an experience to measure the degree of protection with any precision. Although the incidence of non-paralytic illnesses with isolation of virus was lower in vaccinated than in unvaccinated, the reduction was not significant. There was insufficient evidence on which to judge the effect of one injection only.

Owing to the shortage of vaccine and the relatively mild epidemic of poliomyelitis in the summer and autumn of 1956, the assessment of poliomyelitis vaccine has had to be based on a small experience. Nevertheless, the results show that there was some protection in both pre-school and school children, and that the Brunenders strain, used in the British vaccine as a substitute for the virulent Mahoney strain incorporated in American vaccines, conferred protection against type I infections.

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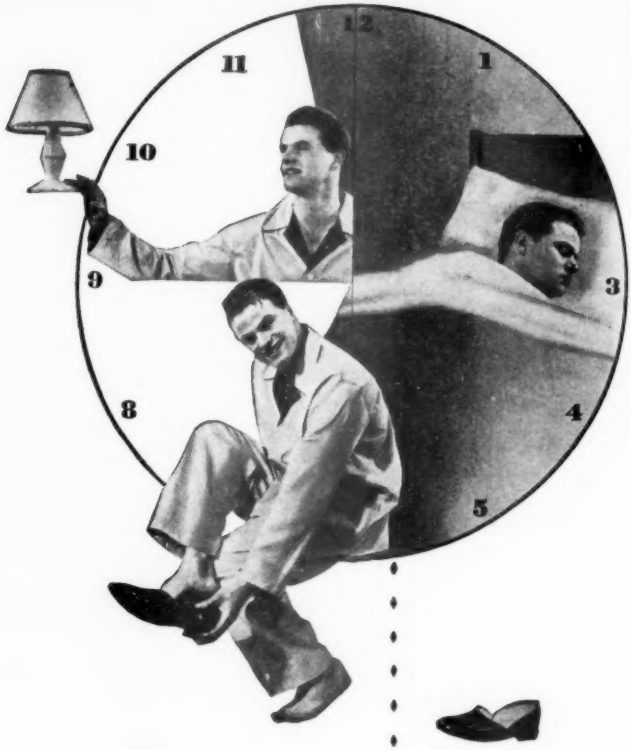
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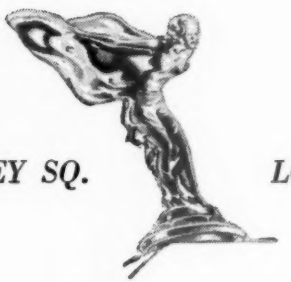
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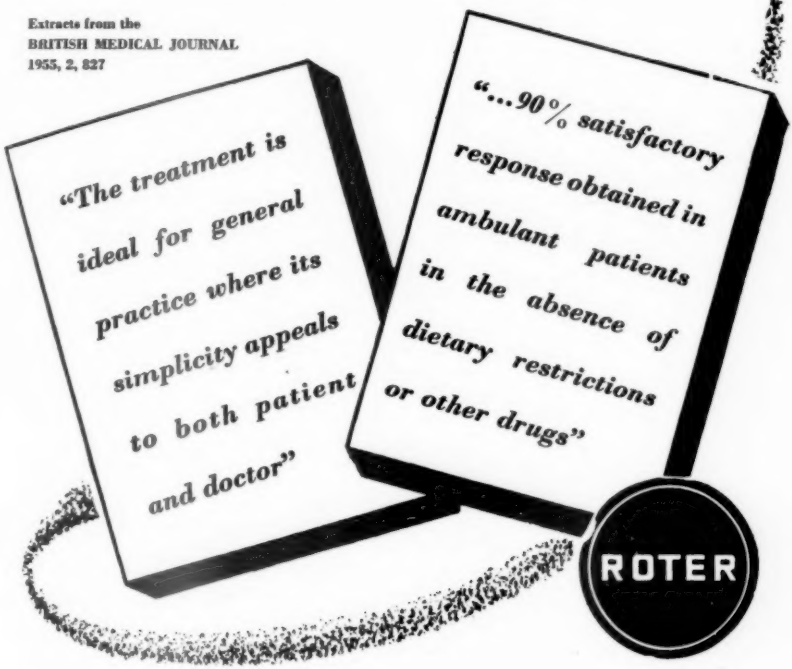


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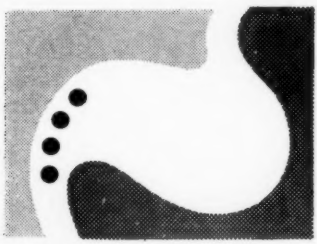
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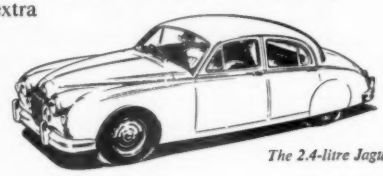
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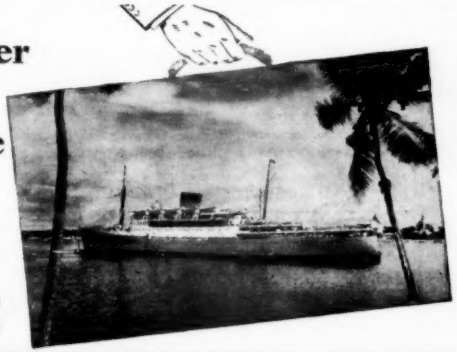
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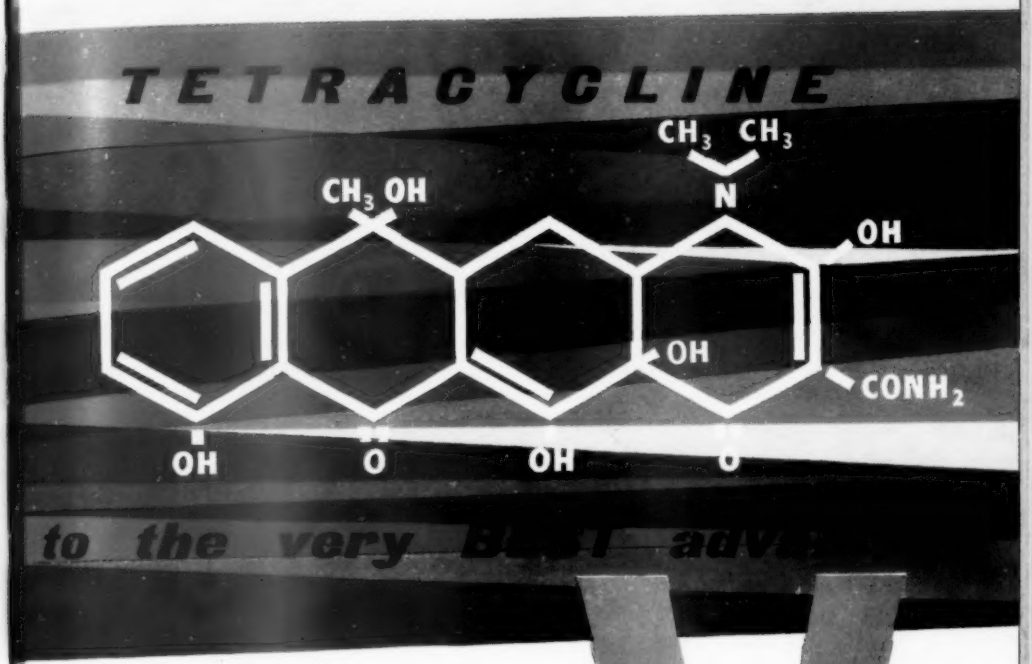
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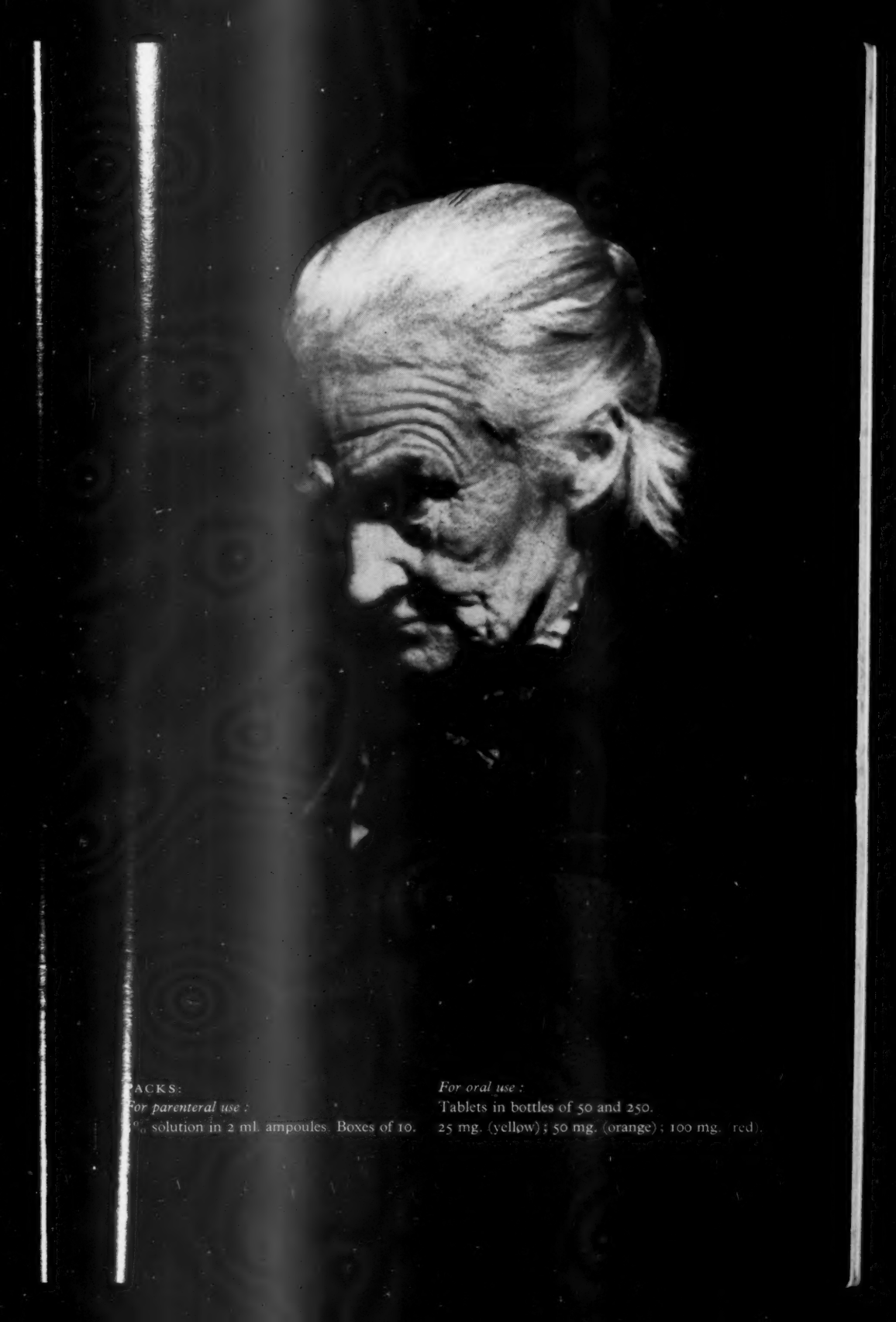
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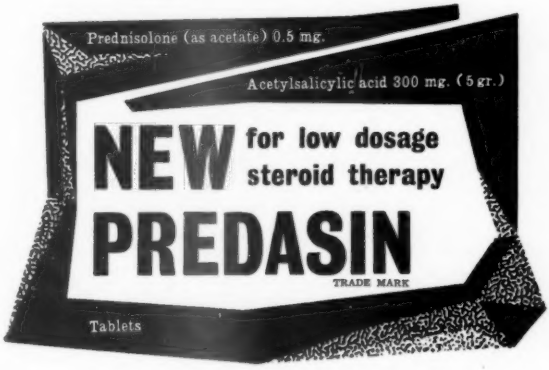


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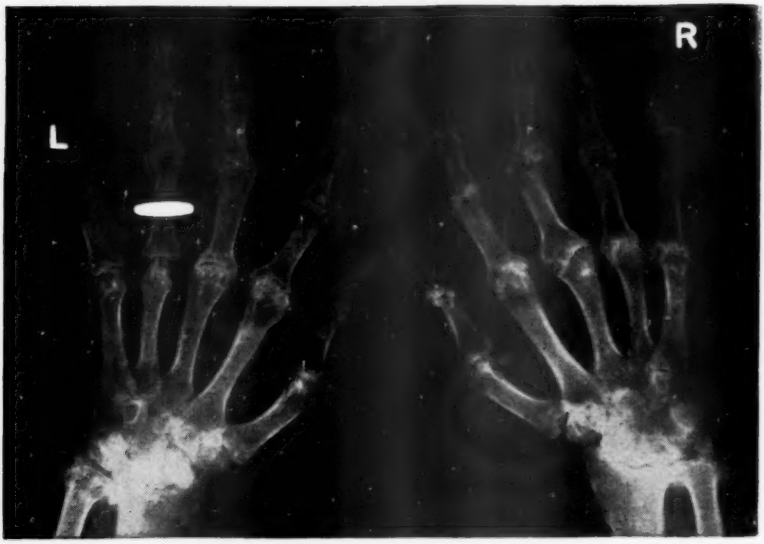
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1 (*Bufferin in the Management of Rheumatoid Arthritis, J.A.M.A. 158: 386 (June 4) 1955.*)
2 (*The Neutralization of Gastric Acidity with Basic Aluminium Aminoacetate, J. Pharmacol. and Expera Therap. 82:247 (Nov.) 1944.*)
3 (*In Vitro Differences Between Dihydroxy Aluminium Aminoacetate and Dried Aluminium Hydroxide Gel, J. Am. Pharm. Assoc., Sc. Ed. 41:361 (July) 1952.*)
4 *Effect of Buffering Agents on Absorption of Acetylsalicylic Acid, J. Am. Pharm. Assoc., Sc. Ed. 39:21 (Jan.) 1950.*)
5 (*The Pharmacologic Principles of Medical Practice, ed. 3, Balto., The Williams & Wilkins Company, 1954, p. 593.*)

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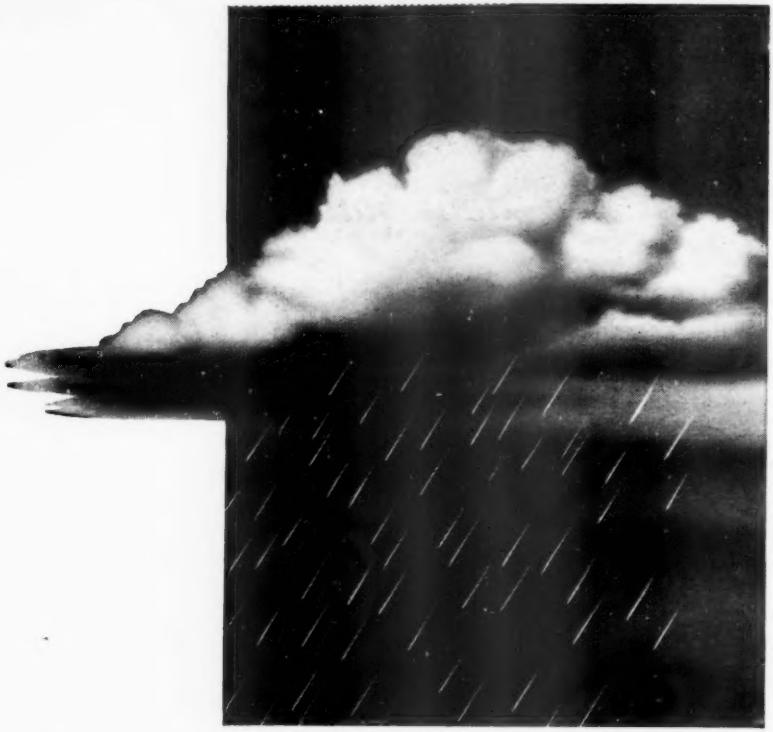
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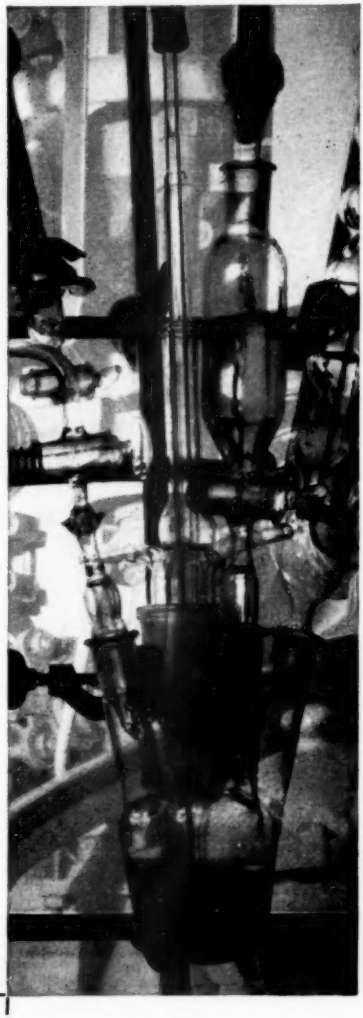
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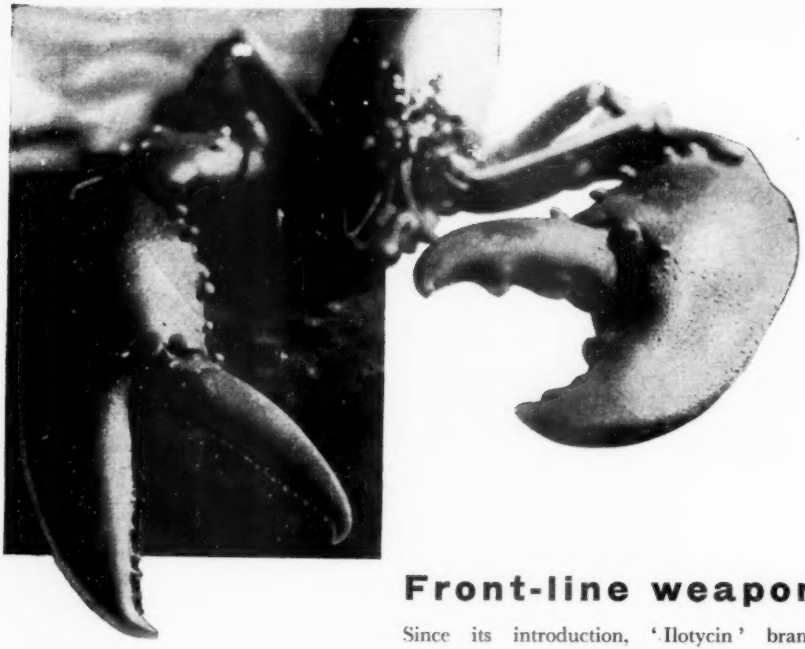
Brit. med. J. (1956) 1, 1159

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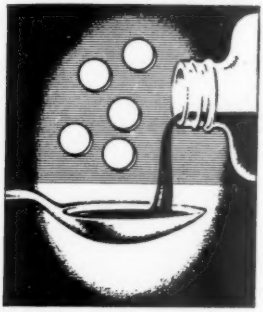
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*Sce n Brit. Encyclopaedia of Medical Practice, Interim Supplement, Jan. 1957, p. 12.



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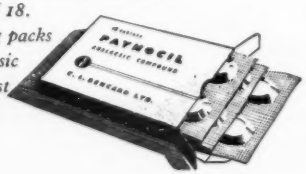
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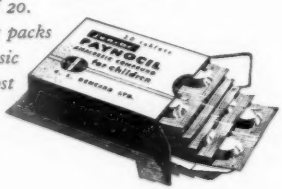
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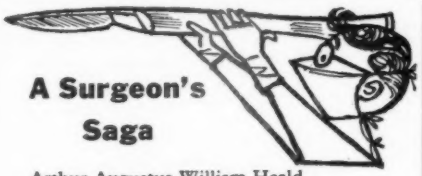
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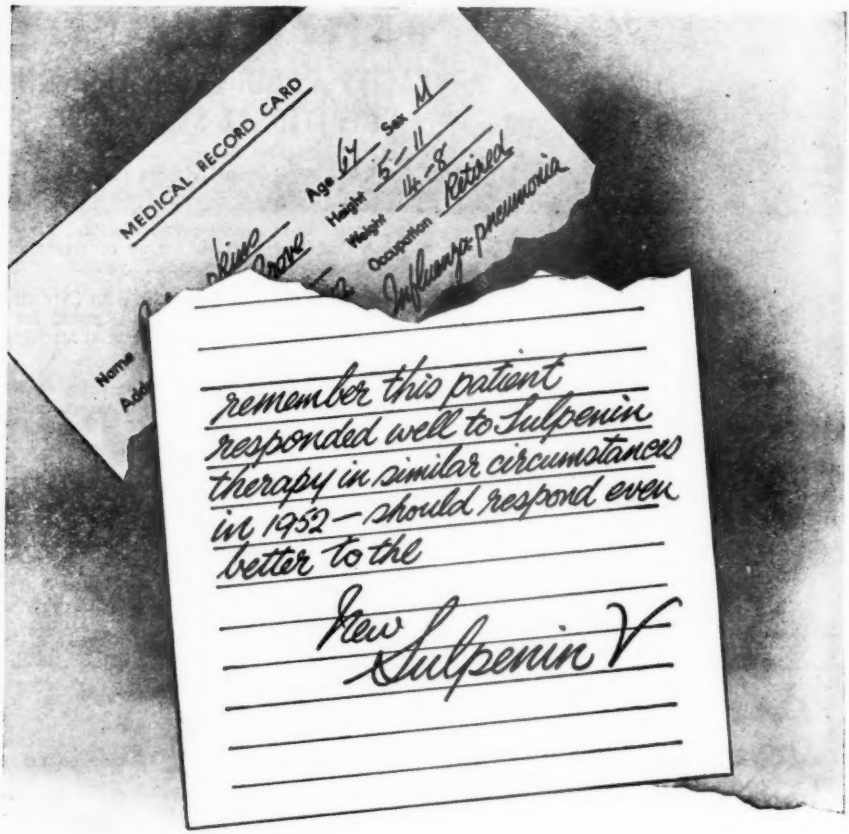
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